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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

PC
900177

SEP 23 1983

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

TO:

R. Mountfort, PM # 23
Herbicides/Fungicides Branch
Registration Division TS-767

THRU:

William L. Burnam, Chief *WLB 9/22/83*
Toxicology Branch
Hazard Evaluation Division TS-769

Subject: PP # 4F1486: Dimethyl Sulfoxide (DMSO). Amendment for use on peas with carbaryl and diazinon. Proposal for a Specific Exemption under 180.10XX.

Caswell #: 381

CAS RN: 67-68-5

P796

Use: Solvent

Limits: On growing peas with carbaryl and/or diazinon.

Sponsor: Crown Zellerbach, Cama, WA.

Recommendation:

Toxicology Branch has no objection to a Specific Exemption for the use of DMSO on growing peas in combination with carbaryl and/or diazinon. We agree with the form as proposed by RCB in their 9/3/83 review; we would only add that the CAS Registry Number (67-68-5) be included.

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Bases for the Recommendation:

1. Food Uses of DMSO.

DMSO has an indirect food additive tolerance of 0.01% as residual solvent in polyethersulfone resins under 21 CFR 177.2440. There is also a tolerance of 50 ppm in polysulfone resins under 21 CFR 177.2500.

2. Toxicity

Numerous clinical and animal toxicity studies were examined in earlier reviews of this petition. The Toxicology Branch concluded that the use of DMSO as an inert solvent in pesticide formulations was appropriate.

Studies that support exemption of DMSO from the requirement of a tolerance include (from our memo of 9/8/78, D. Ritter):

- Monkey 18 month oral ingestion NOEL = 3.0 gm/kg/day
- Dog 8 month oral ingestion NOEL = 3.0 gm/kg/day
- Dog 6 month oral NOEL = 2.5 gm/kg/day
- Rat teratology NOEL - negative at up to 12 gm/kg

In addition, there is an excellent internal Branch review (Larry Anderson, Ph.D., 7/27/79) of all relevant toxicity studies and clinical studies that were then available. Overall, the toxic effects of DMSO in animals and man are limited to extremely high levels of exposure, in the Gram-per-Kilogram of body weight range as demonstrated by the data above. The most unusual of these effects was the appearance of certain lens changes in the dog (at 2.5 and 5 gm/kg/day), swine (at 2.7 and 4.5 gm/kg/day applied dermally) and in rabbits (at 2.7 ml and 8.1 ml of a 90% solution applied dermally). Man is not affected.

In our most recent review of DMSO we recommended that additional toxicity data were needed in support of a general tolerance of 10 ppm in all crops; 0.3 ppm in meat, eggs, poultry and meat byproducts, and 0.15 ppm in milk (review of 7/24/79, K. Bailey). However, since the present request involves only the rac peas (with pods), and since DMSO residues, if any, will be < 1 ppm, and since DMSO background levels may be as high as 16 ppm, we are not now seeking additional toxicity data on DMSO per se.

Overall, we consider that the toxicological data requirements for exemption under 180.100(d) have been met.

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3. Residues

RCB have concluded in their review of 9/3/83, R. Perfetti, that:

- ° Residues of DMSO in peas per se will be less than 1 ppm. Residues will range from 2.7 to 17.5 ppm in the foliage. Foliage is not a human food item.
- ° The presence of DMSO had no effect on residues of diazinon or carbaryl.
- ° Background levels of DMSO in rags as well as processed foods were 0 to 16 ppm.

4. Applicator Safety

Applicator Precautionary labeling must be based on standard acute testing of any new formulations containing DMSO i.e., oral LD₅₀, dermal LD₅₀, dermal irritation, eye irritation and inhalation LC₅₀, if applicable.

David L. Ritter 9-16-83

David L. Ritter, Acting Section Head
Rev. Sec. # 1/Toxicology Branch
Hazard Evaluation Division TS-769

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

9/8/83
SEP 8 1983

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM:

SUBJECT: PP#4F1486 DMSO on Various Crops. Amendment of
4/25/83.

FROM: *R. B. Perretti*
R. B. Perretti, Ph.D., Chemist
Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

THRU: Charles L. Trichilo, Chief
Residue Chemistry Branch *R. D. Schmitt*
Hazard Evaluation Division (TS-769)

TO: Product Manager No. 23 (R. Mountfort)
FHB, RD (TS-767)

and

Toxicology Branch
Hazard Evaluation Division (TS-769)

This amendment is in response to a conference held on 11/17/82 in which the petitioner was advised of the following with regards to a request for a specific exemption for DMSO.

1. The only data requirement would be for residue data on the active ingredient in the formulation containing DMSO which would demonstrate that there would be no enhancement of residue levels of the active ingredient when DMSO was present versus when formulations not containing DMSO were used.
2. The exemption would be specific for crops which had previously established tolerances for the active ingredient.
3. The comparison of residue level experiments should reflect the maximum proposed use for the active ingredient.
4. If enhancement of residue levels of the active ingredient is observed when DMSO is present, higher tolerance levels for the pesticide would be needed before a DMSO containing formulation could be applied.
5. The specific exemption should be in terms of DMSO used with a specific active ingredient on the specific crops for which tolerances are established and comparative residue studies are submitted. As the specific active ingredient obtains tolerances on additional crops this crop can be added to the exemption provided comparative residue data or residue data employing the DMSO formulation is submitted for review.

This amendment requests an exemption from the requirement of a tolerance for DMSO when used with carbaryl or Diazinon on peas. (This differs from the previous request which proposed tolerances on all crops, meat, milk, poultry and eggs.)

The petitioner has submitted 3 analytical methods for analysis of DMSO in plant tissue. The first two of these have been reviewed previously in conjunction with PP#1E1017 and the subject petition. The third method involved blending with methanol, filtration, and stripping of the methanol in vacuo. The sample is marked with hexane and then continuously extracted with chloroform for 22 to 24 hours. The chloroform solution is evaporated to ca. 1 ml and the solution is diluted to volume with methanol. Analysis is via glc using a flame photometric detector equipped with a sulfur filter.

Validation data for DMSO reflected fortification of various crops with 0.1 or 1.0 ppm of DMSO. Recoveries corrected for blank values ranged from 70 to 170% with blank values ranging from a trace to 3.7 ppm.

While the precision of this method appears to be somewhat inadequate in light of the proposed exemption we are raising no questions with regards to an enforcement procedure at this time.

Diazinon or carbaryl residues in various crops were determined using Official Methods of Analysis AOAC 29.001 and 20.082 respectively.

Recoveries of peas and foliage fortified with 0.1 to 10 ppm of Diazinon ranged from 83 to 96% and from 90 to 98% respectively blank values were all <0.01 ppm. Peas and pea foliage fortified with 0.05 to 10 ppm of carbaryl gave recoveries of 60 to 116% and 73 to 94% respectively. Blank values for peas were 0.01 to 0.03 ppm and for foliage 0.1 to 0.11 ppm.

Residue data for DMSO in various crops involved one application of 5 lb DMSO/acre to various crops. Residues ranged from a trace in peaches, onions and bears to 246 ppm in swiss chard with PHI's of 0 to 10 days (Note: The 246 ppm in Swiss Chard decreased to 0.22 ppm after 10 days. The next highest residue on another crop was 67 ppm on alfalfa at 0 days.)

Analysis of untreated samples for DMSO was published in J. Agric and Food chem 29 No. 5, p 1089 (1981) and showed residues of DMSO occurring on a variety of r.a.c.'s as well as processed foods in the range of non-detectable to 16 ppm.

Pea plants were treated with Diazinon and carbaryl with and without DMSO added to the spray mixture (Five or 15 lb per acre of DMSO was applied to peas.) Diazinon was applied at a rate of 0.5 lb active ingredient per acre and samples of peas and foliage were taken at 0, 1, 2, 6 and 10 day PHI's. DMSO residues in peas (with pods) and foliage ranged from 0.11 to 0.96 ppm and from 2.3 to 17.5 ppm respectively. Residues of Diazinon in treated peas were <0.01 or 0.01 ppm regardless of whether DMSO was present or not. Residues in foliage ranged from 0.22 to 11.6 ppm when no DMSO was present and from 0.22 to 12.8 ppm with added DMSO. It is our judgement that no significant difference between residue levels on peas and pea foliage occurred when DMSO was applied to peas in conjunction with Diazinon.

Residues of carbaryl in peas treated without added DMSO ranged from non-detectable to 0.07 ppm for shelled peas and from 0.23 to 49.2 ppm in foliage with 0 to 10 day PHI's. Residues of carbaryl in peas and foliage when DMSO was added to the spray solution at rates of 5 or 15 lb/acre ranged from non-detectable to 0.12 ppm (15 lb DMSO rate) and from 0.31 to 51.6 ppm respectively. Again we do not consider there to be any significant difference between residue levels of carbaryl in peas and pea foliage when DMSO is applied.

The International Tolerance sheet is attached. There are no Codex or foreign specific exemptions for DMSO, therefore no compatibility questions exist with this petition.

Conclusions

1. In light of this request for a specific exemption no questions are being raised with respect to the analytical method for DMSO at this time.
2. No significant differences between residue levels of Diazinon or carbaryl in peas was observed when DMSO was added to spray solutions of these pesticides.

Recommendation

TOX and EAB considerations permitting we recommend that a specific exemption for DMSO used in conjunction with Diazinon or carbaryl on peas be established. When and if this exemption is published it should read as follows:

Dimethyl sulfoxide is exempted from the requirement of a tolerance when used as an inert solvent in formulations with the following pesticides and on the specific crops listed in accordance with good agricultural practices.

- (a) carbaryl - peas
- (b) 0,0-Diethyl 0-(2-isopropyl-6-methyl-4-pyrimidinyl) phosphorothioate - peas.

Note to PM:

The petitioner should be informed that any expansion of this specific exemption to other pesticides or crops will require data as was submitted for carbaryl and Diazinon on peas.

TS-769:RCB:R. Perfetti:cdw:CM#2:Rm810:x77324:8/30/83
cc: R.F., Circu, Reviewer, TOX, EEB, EAB, Petition No. PP#4F1486
FDA, Robert Thompson
RDI: R.S. Quick, 8/30/83; R. Schmitt, 8/30/83

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

NOV 17 1982

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMO OF CONFERENCE - Held on 11/3/82

Attendees:

R.B. Perfetti, RCB, HED
S. Mosher, Crown Fellerbach
D. Hepler, " "
R.B. Bailey, " "
H.B. Lackey, " "
O.E. Paynter, Tox Branch, HED
D. Ritter, " " "
R. Mountfort, HFB, RD
T. Ellwanger " "

The petitioner came in to discuss PP#4F1486 dimethylsulfoxide (DMSO) on various crops. The following were our answers regarding a request for a specific exemption for DMSO.

- 1) The only data requirement would be for residue data on the active ingredient in the formulation containing DMSO which would demonstrate that there would be no enhancement of residue levels of the active ingredient when DMSO was present versus when formulations not containing DMSO were used.
- 2) The exemption would be specific for crops which had previously established tolerances for the active ingredient.
- 3) The comparison of residue level experiments should reflect the maximum proposed used for the active ingredient.
- 4) If enhancement of residue levels of the active ingredient is observed when DMSO is present, higher tolerance levels for the pesticide would be needed before a DMSO containing formulation could be applied.
- 5) The specific exemption should be in terms of DMSO used with a specific active ingredient on the specific crops for which tolerances are established and comparative residue studies are submitted. As the specific active ingredient obtains tolerances on additional crops this crop can be added to the exemption provided comparative residue data or residue data employing the DMSO formulation is submitted for review.

The conference ended at this time.

TS-759:RCB:RPerfetti:vg:CM#2:Rm:810:X77377:11/16/82
cc: RF, Circ., Perfetti
RDI: Onley, 11/12/82; Schmitt, 11/12/82

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

NOV 17 1982

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PESTICIDES AND TOXIC SUBSTANCES

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The conference ended at this time.

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CrownZellerbach
Chemical Products Division



October 13, 1982

PAGE

Mr. Richard Mountfort
Product Manager (23)
Fungicide-Herbicide Branch
Registration Division (TS-767)
United States Environmental Protection Agency
Washington, D.C. 20460

Dear Mr. Mountfort:

Subject: DMSO Petition 4F1486

This confirms our meeting with you and other members of your Branch, to be held at 11:00 a.m. Wednesday, November 3rd, in the 8th Floor conference room, Crystal Mall Building No. 2. Attending for Crown Zellerbach besides myself will be:

Mr. Sol Mosher, CZ Washington, DC office (phone 202/293-5374)
Mr. H. B. Lackey, Manager of Regulatory Affairs, Crown Zellerbach,
Chemical Products Division, Camas, WA 98607
Dr. Doug Hepler, Toxicology Consultant

We will arrive around 10:45, prepared to discuss informally the data which has been submitted to EPA and to answer any questions you may have.

As a suggested agenda, we could run through a half-hour presentation following the attached outline, prior to a discussion period. If you or your people have specific areas where you perceive a problem needing discussion, it would help us to prepare for the meeting if you could let us know in advance what these are. We would appreciate your comments concerning this proposal.

We look forward to meeting with you.

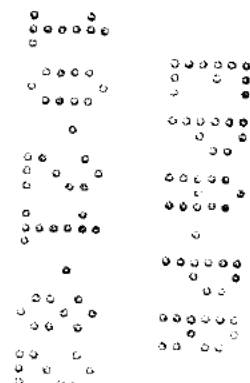
Sincerely yours,

R.B. Bailey
General Manager

R. B. BAILEY/hw

Attachment

cc: Sol Mosher, CZ, Washington D.C.
Thomas C. Ellwanger, Jr., EPA
Dr. John A. Todhunter, EPA



AGENDA FOR DMSO MEETING

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U. S. E. N. T. A. T. E. S. E. N. V. I. R. O. N. M. E. N. T. A. L. P. R. O. C. E. E. D. I. N. G. A. G. E. N. C. Y.

DATE: July 24, 1979

SUBJECT: PP 4F1486-Amendment of 1/16/79, Concerning a Proposed Tolerance for Dimethylsulfoxide (DMSO) on Essentially All Raw Agricultural Commodities

FROM: K. L. Bailey and Larry Anderson
Toxicology Branch/HED (TS-769)

TO: W. Garner
PM #23, HFB/RD (TS-767)

THRU: M. Adrian Gross
Chief, Toxicology Branch/HED (TS-769)

RCB
Guth
Ranbetti
PP 4F1486
9bc
7/25/79
Caswell # 381

Note: This petition is unique in that the proposed tolerances are for an inert ingredient dimethylsulfoxide (DMSO) and not an active ingredient, as is normally the case. In addition, this action is complicated by the unusual chemical and biological properties of DMSO in conjunction with the potential of DMSO to, possibly, markedly enhance penetration of active pesticide ingredients into biological tissue.

I. Petitioner:

Crown Zellerbach Corporation
Comas, Washington 98607

II. Physical/Chemicals data

Structure: $\text{CH}_3-\overset{\text{O}}{\underset{\text{O}}{\text{S}}}-\text{CH}_3$
Mol. Wt: 78.13

Solubility Properties: Most organic compounds and many inorganic compounds are soluble in this unusual solvent which may be considered somewhat of a "universal" solvent.

III. Regulatory History

For details consult the attached memorandum-no date- from J. G. Cummings (Chief, Residue Chemistry Branch) to J. M. Conlon, (Acting Director, HED) concerning DMSO. Among other points, it is to be noted that this J. G. Cummings memo notes PR Notice 323 of 6/6/68, which limits the DMSO concentration of any formulation to 15%.

IV. Proposed Tolerances

Tolerances for DMSO are proposed as follows:

- o 10 ppm in all crops
- o 0.3 ppm in the meat, fat, and meat by-products of cattle, goats, hogs, horses, poultry, and sheep.
- o 0.3 ppm in eggs.
- o 0.15 ppm in milk.

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V. Existing Tolerances

There are no existing tolerances for DMSO. However, it is to be noted that there is an exemption from the requirement for a tolerance for DMSO as per 40 CFR 180.1001 (d) which permits the following uses of DMSO: "Solvent or cosolvent for formulations used before crop emerges from soil or prior to formation of edible parts of food plants."

VI. Conclusion

There are inadequate toxicologic studies available to determine the health hazards associated with this proposed use of DMSO.

In order to adequately assess the toxicologic hazards associated with the use of DMSO the following information is required:

- o A rat and a mouse oncogenic study is required.
- o A rat chronic feeding study is required.
- o A two-generation rat reproduction study is required.

- o As DMSO is a teratogen in the golden Syrian hamster in which no clear NOEL has yet been demonstrated, a teratogenic study in the golden Syrian hamster is required in which a clear NOEL is demonstrated. As there is evidence that DMSO is, possibly, a teratogen in the dog, a teratogenic study in the dog is required to clarify this point.

- o Mutagenic studies may ultimately be required in the future. However, considering that DMSO has clearly been shown not to be a mutagen in numerous Ames Studies, we do not believe such testing is presently warranted.

Future registrations of formulations containing DMSO must be considered toxicologically on a case by case basis.

VII. Toxicology Review

It is to be noted that there is a great mass of toxicology data available in the literature that we are in the process of reviewing. Thus, it is possible that new toxicological concerns may arise upon completion of this review; however, it is apparent that there are serious data gaps which exist in the literature concerning DMSO.

A. Proposed Tolerance

In relation to this proposed tolerance the following toxicity studies are required:

- o Oncogenicity-No adequate oncogenic studies are available. We require two oncogenic studies (a rat study and a mouse study).
- o Chronic feeding-No adequate chronic feeding study is available. We require a rat chronic feeding study.

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- o Reproduction - No adequate reproduction study is available. We require a two-generation rat reproduction study.
- o Teratology - There are teratogenic studies available which indicate that DMSO is a teratogen in the golden Syrian hamster (1)(2) and possibly in the dog (3). The hamster studies are ambiguous in that it is not possible to determine what the NOEL is for DMSO as a teratogen. We require an additional golden Syrian hamster teratogenic study with an unambiguous NOEL; in addition a dog teratogenic study is required to determine whether DMSO is or is not a teratogen in that species.
- o Mutagenicity - The mutagenic testing that is required is not entirely clear at present. However, any mutagenic testing that may be required for this compound in the future should be tempered with the fact that DMSO is commonly used as a negative control in Ames Mutagenic Studies.

B. Registration Actions

While there is inadequate toxicologic information presently available to delineate all of the hazards that may be associated with formulations that contain DMSO, the following points must be considered.

- o DMSO, depending upon the DMSO concentration and the associated solute, has been noted to markedly increase the dermal penetration of certain compounds. We therefore recommend that each and every formulation containing DMSO be considered on a case by case basis and that great caution be exercised in extrapolating any toxicologic information from data where DMSO was either not used or used at a far different concentration.
- o As DMSO and, possibly, associated solutes have been observed to penetrate the kinds of material used in the manufacture of protective equipment such as gloves, there should be adequate information available delineating what type of protective equipment offers an adequate barrier to the penetration of DMSO and associated solutes before a future registration is permitted.
- o As DMSO readily penetrates human skin and as DMSO is a teratogen, considerable thought must be given to determining whether formulations containing DMSO may be safely used. However, as the teratogenic potential of DMSO has not been clearly defined, this point must await future teratogenic testing.

References

1. Ferm, V. H. Teratogenic effect of dimethylsulfoxide.
Lancet 1, 209 (1966).
2. Robens, J. F., Teratologic studies of carbaryl, diaziomon, norea, disulfuram,
and thiram in small laboratory animals, toxicol. Appl. Pharmacol. 15, 152-163
(1969).
3. Review by S. H. Frazier, FDA, for NDA 32-168 (10-24-68).

DATE:

SUBJECT: DMSO, Crown Zellerbach petition 4E1486, (your note 8/29)

FROM: Chief, RCB

TO: J. M. Conlon, Acting Director, HED (TS-769)

The records of this petition have been reviewed as requested. The salient points in the history of the DMSO petitions are summarized along with a statement of the unresolved issues and RCB recommendations.

Chrono

1. 7/28/70, PP# 1E1017 submitted by CZ proposed exemption for DMSO for use on all growing crops. Because of data deficiencies, proposal was reduced to pre-emergence treatments of corn and soybeans only. A regulation (§180.1001(d)) exempting DMSO for this use issued.
2. 2/23/73, PP# 3E1364 submitted by CZ proposed that §180.1001(d) be amended to permit pre-emergence use on all crops. Regulation issued 8/16/73 granting amendment as proposed and is still in effect.
3. 3/20/74, PP# 4E1486 submitted by CZ proposed exemption for application DMSO to all growing crops with 24 hour pre-harvest restriction. Petition is presently in reject status. Chronology follows:
 - 5/7/74, TOX recommends for exemption as proposed
 - 7/24/74, Chemistry Branch recommends against - (inadequate information on nature of residues from foliar sprays).
 - 7/29/74, Environ. Chem. recommends against (no PR 70-15 data)
 - 8/2/74, Company informed petition denied
 - 8/8/74, Petition amended
 - 9/13/74, TOX finds that residues in fruits & vegetables (2 and 6 ppm) are toxicologically significant and recommends that tolerance be considered instead of exemption.
 - 12/2/74, CZ informed petition denied on grounds of TOX, Residue Chemistry, and Env. Chem. deficiencies.
 - 5/16/75, Petition amended
 - 9/16/75, Chemistry recommends against on residue data deficiencies and cites need for tolerance as per TOX recommendation of 9/13/74.

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10/16/75, TOX recommends for exemption contingent on concurrence of Chemistry.

11/20/75, Petition amended to prohibit use on forage crops after emergence.

4/9/76, Chemistry concurs in TOX recommendation for exemption.

7/20/76, Chemistry suggests appropriate tolerance levels as per new RD policy on tolerance for inerts.

10/14/76, TOX replies point by point to CZ and finds exemption appropriate.

12/6/76, RD sends CB chemist to CZ labs to conduct method trial on assumption that tolerance is viable.

12/10/76, PM 23 informs petitioner that exemption denied and cites potentiation with other chemicals. Also informs that tolerance proposal necessary with each DMSO/a.i./crop combination.

1/5/77, Report method trial successful

4/4/77, Chemistry recommends appropriate tolerance levels for crops, eggs, meat, milk.

Subsequent to this there followed a series of correspondence exchanges between PM 23 and CZ which essentially reiterated the positions.

Statement of unresolved issues

1. Exemption vs. tolerance

As the chronology shows, there were several reversals of opinion within the science branches on this point. The first reversal was for scientific reasons. The second was because of new policy regarding regulation of residues of inerts which was under development in OPP at that time. It was prompted by a GAO report which was critical of the Agency's procedure for clearing inerts for use on food crops. The Agency replied in a letter to the Congress that tolerances would be set for inerts (where appropriate). DMSO (and another inert, epichlorohydrin) were appropriate prototypes. Without a detailed analysis of exemptions vs tolerances, the basic criteria are that (a) if the inert requires some use restriction, (e.g., a PHI), in order to reduce residues to a level acceptable to TOX, it should not receive an exemption; (b) if residues could occur through gross misuse, accident, or any reasonable means at some level which could cause injury, it should not receive an exemption. (See also SAB Study Group on Tolerances draft working paper).

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RCB recommendation: The proposed foliar uses of DMSO will produce real and persistent residues in food crops and trace levels in meat/milk/eggs. The exposure to humans should be controlled by tolerances and not an exemption. There are adequate residue data available to support the tolerance recommended in Dr. Hummels' evaluation of 4/4/77.

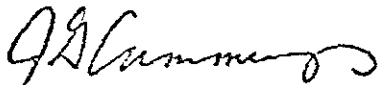
2. Requirement for separate tolerance petition for each DMSO/a.i./crop combination.

The petition record does not show how this requirement arose. It was not from the Science Branches. The letter of 10 Dec. 76 from PM 23 to CZ informing of this requirement possibly was based on discussions between PM 23 and the Pesticide Science Officer, RD. The Science Branches (TOX and CB) stated in their review that possible effects of DMSO on residue levels of a.i. could be handled at time of registration.

Recommendation: Assuming that DMSO tolerances may be set, this "potentiation" of a.i. could be controlled through the registration process, providing that a SOP is set up for RD review staff to do this.

Additional Comment

1. The term "potentiation" has been used in the PM/CZ correspondence to denote an extending effect by DMSO on residues of a.i. This should not be confused with the normal meaning of potentiation in pesticide terminology, which is that the total toxic effects of two chemicals administered together is greater than the sum of the effects when administered separately.
2. RD should clarify whether PR Notice 323, 6/6/68 is still operative. This PR Notice limited DMSO to 15% of any formulation, and required declaration as an active ingredient, among other things.
3. Mr. Ritter (TOX) is preparing a memo summarizing the TOX recommendations. It may be necessary to reconcile still differing opinions on exemption vs. tolerance.



J. G. Cummings
Chief, Residue Chemistry Branch
Hazard Evaluation Division

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of
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6 FEB 1979

FF# 4F1486 Dimethylsulfoxide on crops. Amendment of 1/16/79

R. B. Perfetti, Chemist, Residue Chemistry Branch, HED (TS-769)

Product Manager 23 (W. Garner), Registration Division (TS-767)
and Toxicology Branch

Acting Chief, Residue Chemistry Branch

This amendment is in response to our memo of 4/4/77 (R. J. Hummel) in which RCB stated that we would be able to recommend for the following tolerance levels for DMSO.

10 ppm in all crops
0.2 ppm in the meat, fat, and meat by-products
of cattle, goats, hogs, horses, poultry,
and sheep
0.2 ppm in eggs
0.1 ppm in milk

The petitioner has submitted a revised Section F proposing a 10 ppm tolerance for residues in all crops, a 0.3 ppm tolerance in meat and eggs, and a 0.15 ppm tolerance in milk. These higher (than RCB's recommended) levels are proposed to account for background levels found in meat, milk, poultry and eggs. We suspect this background is ~~very~~ due to vagaries in the method. Regardless, TOX Branch considerations permitting, we recommend that the proposed tolerances be established.

R. B. Perfetti, Ph.D.

TS-769:RCB:WSME:RDPERFETTI:sdb:X62610:RML08:2/15/79

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for Wed. meeting.

DMSO, PP# 4F1486, your memo 9/25/78

J. G. Cummings, Chief, Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

Acting Director, HED (TS-769)

Reply to your questions in the order presented:

1. It is not unusual to have solvents listed as active ingredients on insecticide labeling. However, RD has been unable to locate any record of DMSO as an active ingredient on product labeling.
2. It would be possible to issue a regulation controlling DMSO residues, based on its own toxicological significance and without regard to its effects on active ingredients. The tolerance would necessarily be tied to the agricultural practices employed.
3. It is likely that many solvents and adjuvants enhance penetration of active ingredients through plant and animal membranes. It therefore becomes a matter of degree with DMSO. The reputation of DMSO for this property may be traced to the publicity it received some years ago as a pharmaceutical agent and to the experience of laboratory workers in which it can be tasted in the mouth moments after skin contact.
4. For the reasons explained in the previous memo we believe tolerances could be established for DMSO as an inert.
5. Question 5 is not entirely clear to me. Presumably any formulations containing DMSO would be subject to review at time of registration, where evidence would be required as to whether residues of a.i. were extended, and whether the toxicity of the formulation to applicators was enhanced. RD would have to develop an SOP of this.
6. The Comptroller General report to the Congress (Dec. 1975) pointed out deficiencies in the Agency's procedure for clearing inerts. The Agency's response to the Congress (see attached news clip) included a statement that tolerances were required for inerts if residues remained on foods. To date, a tolerance has not been established for any inert.

The still unresolved issue of tolerances vs. exemptions for inerts is summarized in the attached memo 12/10/75 re epichlorohydrin.

J. G. Cummings

TS-769:RCB:JGCUMMINGS;sdb:x62610:rm108:WSME:10/2/78
cc: Ritter, Inerts (PF), JGC, RF

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

18 SEP 1978

DATE:

SUBJECT: DMSO, Crown Zellerback Petition 4F 1486 - your
 memos of Sept. 8 and undated (from RCB) respectively

FROM: Acting Director, Hazard Evaluation Division

TO: L. B. Dale
 → Joe Cummings

I have reviewed both of your memos on the subject and find that I need some additional information and clarification before making my recommendations to the DAA:

First of several questions to both Branches:

1. Is DMSO ever used as a pesticide by itself? --without "another" active ingredient?
2. If not, is it then possible to postulate the bio-significance of DMSO without consideration of the actives with which it may be used and the actual agricultural practice employed?
3. If DMSO is used in conjunction with other active ingredients, and DMSO functions as a solvent extender, and penetration accelerator, is it likely to have a significant effect on the fashion in which plants or animals react to the active ingredient at time of application?

 If so, is the change in reaction a function of the quantity of DMSO present?
4. If there are sufficient general Residue and Toxicology data to establish a tolerance for DMSO as such, why not do so, instead of issuing an exemption?
5. Would the issuance of an exemption lead formulators to believe that they would not have to consider effect of DMSO on the toxic characteristics of their products?

Would HED staff require users of DMSO in conjunction with A.I., to submit data that demonstrated net effect of formulation as used rather than the A.I. only?

6. Does the basic approach to tolerances, and inerts and exemption as practiced today agree with what we have told GAO, and more importantly, does our approach to inerts give us the right answers vis a vis protection of public health?

If not, why not?

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DATE: SDB

SUBJECT: PP# 4F1486: DMSO exemption from the requirement of a tolerance - response to Congressional inquiry.

FROM: James M. Conlon, Acting Director
Hazard Evaluation Division TS-769 and Douglas M. Campt, Acting Director
Registration Division (TS-767)

TO: Edwin L. Johnson, Deputy Assistant Administrator Office of Pesticide Programs

The Crown Zellerbach Corporation (CZ) submitted a petition in 1974 to exempt from the requirement of tolerance the solvent, Dimethyl Sulfoxide (DMSO) when used as a solvent in formulations of pesticides applied pre-harvest to Raw Agricultural Commodities (racs).

Final action has been delayed on this petition because of unusual properties attributed to DMSO, i.e., that it enhances absorption across plant and animal membranes, may potentiate toxicity of the active pesticide and act as an extender on residues of the active ingredient. Furthermore, there have been opposing recommendations from TOX Br. and Residue Chemistry as to whether DMSO residues should be regulated by a tolerance or by an exemption from the requirement of a tolerance.

A contributing factor to the delays on this petition was the emergence of an internal policy issue on whether the Agency should regulate residues of certain inerts through tolerances or through the exemption procedure. In responding to a GAO report on this matter, the Agency has informed Congress in 1976 that tolerances were required for inerts. However there have not to date been any tolerances established for an inert.

A meeting was held by HED staff on 10/5/78 and it was resolved that:

1. Tolerances for DMSO on crop group basis should issue rather than an exemption.

-2-

2. The tolerance regulation for DMSO will be based on the toxic potential of DMSO itself, and not upon any potentiating effects it might have on active ingredients in the formulations in which it is used.
3. After issuance of the tolerance, the matter of enhancing toxic effects of active ingredient upon spray applicators or its action as a residue extender will be dealt with at time of registration for each a.i./DMSO combination for which registration is proposed. This will require that RD develop a standard operating procedure which would flag all new registration applications for DMSO formations to HED.
4. The RD/PM should draft a regulation proposing the tolerance levels for DMSO as recommended in Dr. Hummel's memo of 4/4/77.

cc: TOX (Dale, Ritter), RCB, RD (Camp, Mountfort)

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CrownZellerbach
Chemical Products Division

January 16, 1979

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ms. Willa Y. Garner
Product Manager 23
Fungicide Herbicide Branch
Registration Division (TS-767)
United States Environmental
Protection Agency
Washington, D.C. 20460

Dear Ms. Garner:

Re: Pesticide Petition No. 4F 1486

We appreciate the Agency's thorough review of the referenced petition and supporting information. The alternative presented by your scientific personnel to establish tolerances in place of the requestion exemption is acceptable in concept. Also, specifically, the 10 ppm level on food crops is acceptable. However, in light of the fact that DMSO is found to be naturally occurring in animal and animal products, we feel the limits proposed on these are too low.

During development of a sensitive analytical method for DMSO in animal and animal products, the chemist from the EPA Chemistry Branch found DMSO naturally occurring in beef liver and milk. Using the attached procedure his results were:

Solvent blank	0.006 ppm DMSO
Milk blank	0.060 ppm DMSO
Beef liver blank	0.095 ppm DMSO

Based on these results, the results of the feeding studies contained in 4F 1486 and toxicology data, we would appreciate consideration of the following tolerances:

10 ppm for all crops

0.3 ppm in meat, fat, and meat byproducts of cattle
goats, hogs, horses, sheep, poultry and eggs.

0.15 ppm in milk

Thank you.

Very truly yours,

J. A. Chapman
General Manager

J. A. CHAPMAN/hw

Mailing Address: P.O. Box 4266, Vancouver (Orchards), Washington 98662
Street Address: 10619 N.E. Coxley Dr. Phone: (206) 254-0924 TWX: 910 474 8663

Bob Hammer
Dave Ritt

To R. Perfetti
for comment
on 2/9/79

RD (Camp) would
like comment before
2/16/79

RD
2/9/79

Chemistry Branch Method for DMSO - Developed by Method Trials Section,
Chemistry Branch, RD

1. Extract with MeOH or 95% EtOH. Extract 30 g of crop with 125 ml methanol (or ethanol) with blending (5 to 10 minutes). Filter through a bed of Celite 545.
(Volume = 150.5 ml if 30 g has 85% water. In case of soybeans and/or other dry crop, add 22.5 ml of H₂O to 30 g of soybeans before extraction with alcohol.)
2. Concentrate a 10 g aliquot (50 ml) to the aqueous phase at 50° C.
3. Transfer the aqueous phase to a 125 sep. funnel and extract with 50 ml petroleum ether or hexane - twice. Discard the solvent.
4. Extract aqueous phase with CHCl₃ (3 x 50 ml) and dry with sodium sulfate.
5. Concentrate CHCl₃ extracts on rotary evaporatory (40° C) to dryness.
6. Make final vol one ml MeOH for GLC analysis.
7. Analyze on GLC system equipped with FPD (sulfur filter). The column used was 6 feet x 3 mm I.D. packed with 15% carbowax 20 M on chromsorb W-AWDMCS - 80/100 mesh. The column was operated at 150° C and N₂ at 100 ml/m.

FOOTNOTES OF CHANGES

- Step 1: For milk and liver, I took 90 g instead of 30 g. Extracted with 250 mls of methanol (distilled in glass). It is better to blend at slow speed, particularly milk, to avoid difficulty in filtration. Took an aliquot of 109 mls which equals 30 g of sample.
- Step 2: Concentrate to the aqueous layer--about 25 to 30 mls.
- Step 3: Extract with 2 x 100 mls hexane (distilled in glass).
- Step 4: Extract with 3 x 75 mls chloroform (distilled in glass) and dry with sodium sulfate.
- Step 5: Take chloroform to about one ml in rotary evaporatory. Transfer to a graduated tube. Two or three additional washes with chloroform. Blow out chloroform with jet of nitrogen (beaker about 40° C). Take to almost dryness. Make to one ml volume with methanol.
- Step 7: Used 20% FFAP/Chrom Q, 60/80. The column was 6 feet. Column operated at 145° C with nitrogen at 95 mls. Detector is 160° C.

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE:

SUBJECT: DMSO, Crown Zellerbach petition 4E1486, (your note 8/29)

FROM: Chief, RCB

TO: J. M. Conlon, Acting Director, HED (TS-769)

The records of this petition have been reviewed as requested. The salient points in the history of the DMSO petitions are summarized along with a statement of the unresolved issues and RCB recommendations.

Chrono

1. 7/28/70, PP# 1E1017 submitted by CZ proposed exemption for DMSO for use on all growing crops. Because of data deficiencies, proposal was reduced to pre-emergence treatments of corn and soybeans only. A regulation (§180.1001(d)) exempting DMSO for this use issued.
2. 2/23/73, PP# 3E1364 submitted by CZ proposed that §180.1001(d) be amended to permit pre-emergence use on all crops. Regulation issued 8/16/73 granting amendment as proposed and is still in effect.
3. 3/20/74, PP# 4E1486 submitted by CZ proposed exemption for application DMSO to all growing crops with 24 hour pre-harvest restriction. Petition is presently in reject status. Chronology follows:
 - 5/7/74, TOX recommends for exemption as proposed
 - 7/24/74, Chemistry Branch recommends against - (inadequate information on nature of residues from foliar sprays).
 - 7/29/74, Environ. Chem. recommends against (no PR 70-15 data)
 - 8/2/74, Company informed petition denied
 - 8/8/74, Petition amended
 - 9/13/74, TOX finds that residues in fruits & vegetables (2 and 6 ppm) are toxicologically significant and recommends that tolerance be considered instead of exemption.
 - 12/2/74, CZ informed petition denied on grounds of TOX, Residue Chemistry, and Env. Chem. deficiencies.
 - 5/16/75, Petition amended
 - 9/16/75, Chemistry recommends against on residue data deficiencies and cites need for tolerance as per TOX recommendation of 9/13/74.

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10/16/75, TOX recommends for exemption contingent on concurrence of Chemistry.

11/20/75, Petition amended to prohibit use on forage crops after emergence.

4/9/76, Chemistry concurs in TOX recommendation for exemption.

7/20/76, Chemistry suggests appropriate tolerance levels as per new RD policy on tolerance for inerts.

10/14/76, TOX replies point by point to CZ and finds exemption appropriate.

12/6/76, RD sends CB chemist to CZ labs to CZ labs to conduct method trial on assumption that tolerance is viable.

12/10/76, PM 23 informs petitioner that exemption denied and cites potentiation with other chemicals. Also informs that tolerance proposal necessary with each DMSO/a.i./crop combination.

1/5/77, Report method trial successful

4/4/77, Chemistry recommends appropriate tolerance levels for crops, eggs, meat, milk.

Subsequent to this there followed a series of correspondence exchanges between PM 23 and CZ which essentially reiterated the positions.

Statement of unresolved issues

1. Exemption vs. tolerance

As the chronology shows, there were several reversals of opinion within the science branches on this point. The first reversal was for scientific reasons. The second was because of new policy regarding regulation of residues of inerts which was under development in OPP at that time. It was prompted by a GAO report which was critical of the Agency's procedure for clearing inerts for use on food crops. The Agency replied in a letter to the Congress that tolerances would be set for inerts (where appropriate). DMSO (and another inert, epichlorohydrin) were appropriate prototypes. Without a detailed analysis of exemptions vs tolerances, the basic criteria are that (a) if the inert requires some use restriction, (e.g., a PHI), in order to reduce residues to a level acceptable to TOX, it should not receive an exemption; (b) if residues could occur through gross misuse, accident, or any reasonable means at some level which could cause injury, it should not receive an exemption. (See also SAB Study Group on Tolerances draft working paper).

-3-

RCB recommendation: The proposed foliar uses of DMSO will produce real and persistent residues in food crops and trace levels in meat/milk/eggs. The exposure to humans should be controlled by tolerances and not an exemption. There are adequate residue data available to support the tolerance recommended in Dr. Hummels' evaluation of 4/4/77.

2. Requirement for separate tolerance petition for each DMSO/a.i./crop combination.

The petition record does not show how this requirement arose. It was not from the Science Branches. The letter of 10 Dec. 76 from PM 23 to CZ informing of this requirement possibly was based on discussions between PM 23 and the Pesticide Science Officer, RD. The Science Branches (TOX and CB) stated in their review that possible effects of DMSO on residue levels of a.i. could be handled at time of registration.

Recommendation: Assuming that DMSO tolerances may be set, this "potentiation" of a.i. could be controlled through the registration process, providing that a SOP is set up for RD review staff to do this.

Additional Comment

1. The term "potentiation" has been used in the PM/CZ correspondence to denote an extending effect by DMSO on residues of a.i. This should not be confused with the normal meaning of potentiation in pesticide terminology, which is that the total toxic effects of two chemicals administered together is greater than the sum of the effects when administered separately.

2. RD should clarify whether PR Notice 323, 6/6/68 is still operative. This PR Notice limited DMSO to 15% of any formulation, and required declaration as an active ingredient, among other things.

3. Mr. Ritter (TOX) is preparing a memo summarizing the TOX recommendations. It may be necessary to reconcile still differing opinions on exemption vs. tolerance.



J. G. Cummings
Chief, Residue Chemistry Branch
Hazard Evaluation Division

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DATE: September 25, 1978
SUBJECT: PP No. 4F1486 - DMSO; HED Acting Director memo of 9/19/78.

FROM: David Ritter, Adjuvant Toxicologist
Toxicology Branch, HED (TS-769)

DLR. 9/25/78

TO: Acting Director
Hazard Evaluation Division (TS-769)

THRU: Acting Deputy Chief
Toxicology Branch, HED (TS-769)

9-25-78

THRU: Acting Chief
Toxicology Branch, HED (TS-769)

This memo responds to the questions raised in your request of 9/18/78 for additional information on DMSO.

1. DMSO as an AI?

There are no registered uses for DMSO as an AI in so far as we are aware.

2. Is it possible to postulate biosignificance of DMSO without regard to Actives?

It is and we have done so. Questions pertaining to specific DMSO/AI formulations are to be resolved at the time of registration.

3. Is DMSO likely to have significant effect on animal and plant reaction to AI?

The available evidence indicates that it does not; reaction to quantity - no more than for any other cleared polar solvent.

4. Why not a tolerance for DMSO?

- a. As presently proposed, any such tolerance would have to be "across the board" without regard to actual residues in specific crops. There are no such tolerances presently extant for AIs*, let alone inerts. This would appear to be in violation of Sec. 409 (c) (4) (A) - tolerances not to be set at a level higher than needed.

- 2 -

a

- b. If we set a tolerance for a safe material like DMSO, we would logically have to gear up to do it for virtually all inerts. This means that full petitions would be needed as for any other tolerance proposal. Last year we addressed some 50 inert requests, and it took only 0.2 MY to do so. If these were all tolerances, a forty to one hundred-fold increase in MY would be needed.
- c. Should the decision be made that tolerances are appropriate for inerts, EPA should publish a proposal in the Federal Register to this end and invite public comment, since it would constitute a significant departure from current practice.

5. Would a tolerance negate formulator considerations?

No. As noted previously, such considerations would be handled at the time of registration, just like any other product. It would be possible to "track" DMSO registrations to insure proper considerations of DMSO products, including enhanced residues and applicator risk.

6. Does our approach to tolerances and inerts agree with what we told GAO?

We personally spent many hours attempting to explain the inerts as well as tolerance programs in Toxicology Branch to GAO investigators. This information was in several instances not passed on the Congress or was misinterpreted. Toxicology Branch was not given an opportunity to comment on the pre-publication draft, something that should have been done. Thus, we believe that the Congress was presented with something other than the whole truth.

We believe that, within the constraints of the limited manpower assigned to the inerts program, we are doing a credible job of protecting the public health from harmful residues of inert ingredients in racs, and from injury to applicators by formulations.

We are not now assessing long and short term environmental effects, although we should be, especially for the more persistent inerts such as the microencapsulating polymers (with parathion); the

- 3 -

the carrier-sticker agents (for gossypure in cotton) and the dimethylpolysiloxane matrix materials (for timed breakdown for a number of AIs - said to be coming into general use in the near future).

Toxicology Branch has made ZBB projections to upgrade the "inerts program" (submitted for FY '76 and '77). At the second increment, we contemplated two additional MYs that could include minimal environmental fate review and additional TOX and RCB review. At the third increment we envisioned up to eight MYs to address all questions now considered for AIs.

Had such a unit been operational at the time DMSO came along, much of the DMSO problem might have been avoided.

Our proposals were not implemented, presumably due to fiscal constraints.

* Mirex and naled are special cases.

cc:
JGCummings
PM #2*3

C.F.W. 9/25/78

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Subject: PP# 4F18486: DMSO exemption from the requirement ~~from~~ of a tolerance - response to Congressional inquiry.

From: James M. Conlon, Acting Director
Hazard Evaluation Division TS-769

and

Douglas M. Campt, Acting Director
Registration Division TS-767

PRIORITY

To: Edwin L. Johnson Deputy Assistant Administrator
Office of Pesticide Programs

The Crown Zellerbach Corporation (CZ) Submitted a petition on 1/19/74 to exempt from the requirement of tolerance the solvent, Dimethyl Sulfoxide (DMSO), when used ^{as a solvent} in formulations of pesticides applied ^{Pre-harvest} to Raw Agricultural Commodities (racs), ~~as a solvent; co-solvent,~~ pursuant to 40 CFR 180.100 were ^{in response} ~~in response~~ (TOX). A number of questions ~~raised~~ raised by the Toxicology Branch and the Chemistry Branch (now designated as the Residues Chemistry Branch - RCB) relating to actual residues of DMSO in racs, and, ^{alleged} by reason of the propensity of DMSO to ~~enhance~~ enhance absorption of other materials, such as drugs, across skin membranes in man and animals, ^{to} enhanced or increased remaining residues of pesticide active ingredients (AIs) following application to racs pursuant ~~xxx~~ to provisions of the Federal Food and Drug, and Cosmetic Act (FFDCA) sections 408 and 409. The attached reviews from TOX and RCB adequately summarize the history of subsequent actions taken with respect to the proposed exemption. The matter boils down to the following:

1. ~~TOXxxxxxxx~~ Although the original ~~xxxxxxx~~ proposal was for an exemption from the requirement of a tolerance, ^{for an} (e.g., ~~clearance of~~ ^{clearance of} inert ingredients from the requirement of tolerance).

-2-

(Crop Group Basis) 049

the RCB is recommending that tolerances up to 10 ppm be established for reasons specified in the J.G. Cummings memo's of 9/7/78 and 10/2/78, PP#4F1486. This is the first instance for tolerances for "inert ingredients" of pesticide formulations and represents a fundamental departure from past policy and practice.

2. TOX remains unpersuaded that tolerances for residues of DMSO ~~are~~ in crops are appropriate for the reasons detailed in the D. Ritter memos of 9/8/78 and 9/25/78, PP#4F1486. They consider that an exemption from the requirement of a tolerance is appropriate. Division, The Acting Director, Hazard Evaluation has carefully considered both positions and finds that there are good arguments supporting ~~each of~~ the respective recommendations of each Branch. He has concluded that reconciliation of the differing views does not appear to be possible at present.

Accordingly, for the reason(s) noted below, AD/HED is recommending, and AD/RD is concurring, that tolerances be established for the solvent, Dimethyl sulfoxide, on crop-group basis, ~~a~~ such tolerance levels to be determined by RCB as appropriate and upon receipt of such ~~infor~~ relevant information as may be required. This recommendation is

based upon the following considerations:

(Joe, fill in please.)

~~Ad/HED and AD/RD recognize that TOX/HED ~~is~~ does not concur in this~~

~~Recommendation Decision~~

~~Recommendation~~
The TOX branch will, however, concur in this action.

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: September 8, 1978

SUBJECT: PP #4F1486 - Dimethyl Sulfoxide (DMSO), exemption from the requirement of a tolerance.

FROM:

FROM: Adjuvants Toxicologist

TO: Toxicology Branch, HED (TS-769)

D.L.R. 9/12/78

TO: Acting Director

Hazard Evaluation Division (TS-769)

THRU: Acting Deputy Chief

Toxicology Branch, HED (TS-769)

*S. L. Chan
(neg!)*

THRU: Acting Chief

Toxicology Branch, HED (TS-769)

[Signature]

This is in response to your "Note to" of 8/29/78 concerning resolution of the DMSO petition noted above.

DMSO Background

DMSO is a solvent that possesses several unusual properties, among these being the propensity to rapidly and massive penetrate the skin. Within seconds, the individual experiences a garlicky taste or presence in his mouth that has been described by some as unpleasant. This property quickly to cross the dermal barrier was exploited during the 60's as a means of administering drugs topically, the theory being that such rapid penetration of skin would perhaps be a means of carrying large amounts of therapeutic agents into the body, especially at sites where there were injuries, e.g., a strained muscle, carcinomas, etc. This has proven to be unfeasible, however, and attempts to administer most drugs per se dermally in DMSO have largely failed. For practical purposes DMSO does not enhance drug absorption across the skin to any significant degree, although much clinical work is still being conducted.

DMSO Mammalian Toxicity

The toxicity of DMSO in mammalian systems is very low:

1. Monkey 18 mo. oral NEL = 3 gm/kg/day
2. Dog 8 mo. oral NEL = 5 gm/kg/day
3. Dog 6-mo. oral NEL = 2.5 gm/kg/day (w/lens changes at highest dose)
4. Swine 90 day dermal NEL = 8 ml/kg/day (w/lens changes)
5. Rat teratology negative at up to 12 gm/kg

- 2 -

6. Rat oncogenesis negative at 50 ppm in drinking water
7. Comparative Pesticide Toxicity - DMSO used as a solvent did not material increase the oral LD₅₀ toxicity of thiram, dieldrin, parathion, carbaryl or MC-A-600 in female rats when compared to that of corn oil and water.
8. Clinical experience - only 1 of 43 patients treated with DMSO for up to 21 months dermally showed evidence of lens effect; this could have been due to pre-existing pathology.
9. Antigens dissolved in DMSO penetrate the skin of volunteers no deeper than the horny layer; the degree of penetration appears to depend on the molecular weight of the antigen.
10. DMSO is the carrier/solvent of choice in the Ames test for mutagenicity.

A large body of clinical experience indicates that DMSO enhances dermal absorption of some drugs and therapeutic agents; produces localized dermatitis; an occasional allergic reaction and halitosis.

The ADI in man is 150 mg/day based on the 18 month monkey NOEL of 5000 mg/kg/day and an 8 month dog study NOEL of 5000 mg/kg using a very conservative safety factor of 2000-fold.

While not at all exhaustive, the above outline demonstrates the extremely low toxicity of DMSO from oral and dermal exposure in mammals. For a more exhaustive treatment of the experience with DMSO please see ANNALS OF THE NEW YORK ACADEMY OF SCIENCES 141:1, pp. 1-671, 3/15/67, C.D. Leake, Ed. and Ann. N.Y. Acad. Sci., 243, 1/27/75, Jacob & Herschler, Eds.

Toxicology Branch Position

TOX/HED cannot support the 12/10/77 R. Mountfort letter to Crown Zellerbach (CZ, the petitioner) for the following reasons:

Require "potentiation" of Residues Studies

1. The petition is a request to exempt DMSO per se from the requirements of tolerance as an inert ingredient (solvent) pursuant to provisions of Sec. 408 and 409 of Federal Food, Drug and Cosmetic Act (FFDCA). Such exemptions for "inerts" are based on a finding of no hazard

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when the material is used in accordance with good agricultural practice, i.e., when the label directions are followed [conditions of proposed use - sec. 409 (b) (1)].

In our review of 11/25/75, D. Ritter, we concluded that the proposed exemption was safe and would protect the public health. The Mountfort letter stipulates that additional data on various combinations of DMSO with active ingredients (AIs) "...are needed to show that existing tolerances (for actives) - parentheses mine - would not be exceeded...".

Our Comment

RCB and TOX agreed with CZ that the question of potentiation of residues could be handled at the time of registration of the new individual formulations. See the R. Beyak memo of conference, 1/23/75.

Our position is unchanged on this issue.

Our reasons for requiring potentiation data from the registrant rather than from CZ in connection with the proposed exemption are as follows:

1. It puts the burden of proof for safety and its attendant costs upon the registrant, where it more properly belongs;
2. It will provide additional toxicity data for the actual formulations per se;
3. It will make the registrant responsible for formally petitioning the Agency for a tolerance that needs to be raised.
4. To require CZ to provide residue data on various AI-DMSO combinations would seem to ignore two important considerations:
 - a. CZ is not in the formulating business and probably does not have the expertise nor the resources to conduct the extensive and costly studies needed. (We have not asked other prime solvents suppliers to do this in the past). Anything provided along these lines by CZ would of necessity be only speculative.

- 4 -

- b. Formulators are not likely to divulge their formulations to CZ because of Trade Secret considerations.
- c. Formulators in any case will have to provide the data on their product at the time of registration regardless of whether CZ also provides data.

2. Tolerances for DMSO as an inert ingredient

TOX addressed this question in the 10/16/75 memo of D. Ritter. We concluded that tolerances were not appropriate, based on the extremely low level of mammalian toxicity. RCB essentially agreed with this position in their memo of 4/9/76, R. Hummel.

Our Comment

EPA has not established tolerances per se for adjuvant chemicals; rather, we have exempted such adjuvants from the requirement of a tolerance pursuant to provisions of 40 CFR 180.1001 and ff.

The procedures, criteria and considerations used by the Adjuvants Toxicologist in making recommendations for adjuvant or inert chemicals are summarized in the attached memorandum of 2/24/77, D. Ritter. These requirements are different in some respects from those used to qualify AIs for actual residues tolerances; this is due principally to policy and fiscal considerations.

TOX has made many recommendations to clear adjuvants including highly polar solvents, without requiring the massive amounts of TOX data submitted in support of the present proposal. These include hydrofurfural alcohol, dipropylene glycol, etc. More often than not, such clearances were granted upon the receipt of a letter and appropriate application of the principles noted in the above cited memo.

On the basis of the comparative toxicities of these solvents themselves, it would appear that DMSO is not being treated fairly by requiring a tolerance without requiring one for the others.

RCB's position respecting tolerances for inerts as we understand it is as follows: TOX is saying in effect that any amount present on the rac is safe when an inert is exempted. A tolerance, on the other hand, is an indication that a residue above tolerance is not safe; hence, establishing a tolerance for an inert is more appropriate, especially if a limitation, such as a 24 hour PHI, is needed.

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This position appears to include a margin for at least some forms of misuse or other contamination.

TOX, on the other hand, holds the countervailing view:

A "Tolerance" is an effective means of controlling pesticide use and thereby protects the public health. A tolerance is not an index of actual exposure. As noted above for inerts, tolerances are established on the basis of conditions of proposed use. Accordingly, a tolerance (and by reference, an exemption) should not be established to cover a possible misuse. We believe that the whole reason for tolerances is to protect against misuse, with severe penalties (crop seizure by FDA) when it occurs and is detected. If applicators were to discover that they can apply, say, 2X or 3X and not get residues over the tolerance limit, then it seems to us that the potential for misuse in the field is greatly increased. [Sec. 409(c)(4)(A) requires that a food additive tolerance, and by reference, a pesticide or inert residue, shall not be set at a level higher than that needed to accomplish the intended effect].

Accordingly, TOX recommendations for clearance of inerts applies only to the extent that good agricultural practice is followed. In effect, we are saying that the exemption is safe and will protect the public health, if and only if the material has been applied in accordance with good agricultural practice. By law, any other mode of application could result in violative residues, subject to appropriate enforcement action.

Does the above mean that TOX considers that any residue resulting from misuse is unsafe? Normally not. That's why we apply safety factors to inerts, when the evidence seem to warrant it. As noted above, the safety factor for DMSO is 2000-fold based on a chronic feeding NOEL. Thus, any conceivable misuse or accidental exposure would be without hazard from a DMSO residue standpoint, and therefore, an exemption, not a tolerance, is appropriate.

A Brief Chronology of PP #4F1486, Exemption for DMSO

1. Petition filed 4/10/74, L. Zink.
2. TOX recommends favorably for exemption, 5/2/74, C. Williams,
3. RCB requests additional residue data 7/24/74, R. Beyak,
4. TOX concurs w/RCB re data; refers question of increased AIs; need for tolerances, 9/7/74, D. Ritter,

- 6 -

5. Memo of conference, CZ, TOX, RCB - AIs to be handled at registration, 1/23/75, R. Beyak.
6. CB requests additional residue data, 9/16/75, R. Hummel.
7. TOX now recommends exemption - safety OK, 10/16/75, Ritter.
8. Limitations increased by amendment, 11/16/75, R. Mountfort.
9. TOX OKs restriction increase, 11/25/75, D. Ritter.
10. RCB OKs " " , 4/6/76, R. Hummel.
11. RCB now requests tolerance, 7/20/76, R. Hummel.
12. CZ letter objecting to tolerances, 8/16/76, Chapman.
13. TOX comments re CZ objections - agrees with CZ, 10/19/76, D. Ritter.
14. RCB requires potentiation data due to PSO, 4/4/77, R. Hummel.
15. RD now needs data for each combination with AI; exemption precluded, 12/10/77, R. Mountfort.

Potential Impact on Public Health

1. Due to the demonstrated extremely low level of toxicity of DMSO we would expect no increase in risk to public health as a result of the proposed use, including an exemption.
2. The Pesticide Applicator could benefit from using DMSO to replace more acutely toxic solvents such as xylene, toluene, diesel oil, etc. Moreover, the applicator would have a built-in "signal" should he inadvertently splash some DMSO-bearing formulation on his skin - he would taste the DMSO within seconds of the accident and could take corrective measure very quickly. This would be advantageous in the case of very toxic materials such as the widely used parathion or aldicarb preparations.

Any potential for increased toxicity due to DMSO in combination with an AI will be assessed at the time of registration of the product.

- 7 -

Recommendations for handling possible instances of DMSO potentiation

1. Assuming that all petitions, registrations and amendments upon receipt in OPP pass through an initial clearing and tracking unit, such as the old RET, we could:
 - a. Let the application be examined to determine whether DMSO is in the formulation. If not, track routinely.
 - b. If DMSO is present, RET will flag for comment to RCB as to adequacy of supporting data; whether supporting tolerances are needed. If not, return application with note to RET.
 - c. If additional or increased tolerances are needed, RCB informs RET or appropriate PM and requests tolerance petition, etc.

David L. Ritter

R/D Init: REngler 9/7/78

A. F. W. 9/2/78

End
of
Document

E N V I R O N M E N T A L P R O T E C T I O N A G E N C Y

AUG 29 1978

NOTE TO: Lamar Dale

Joe Cummings

SUBJECT: Crown Zellerbach Petition 471486 Requesting an Exemption
from the Requirement for a Tolerance for DMSO

Attached is a copy of subject memo which I received from Ed Johnson in which he directs that we conduct a full review of the DMSO problem, with joint RD/HED recommendations in his hands by September 22. As a first step toward providing that recommendation, I would like you to review the appropriate records and data and provide me with a joint recommendation by September 15.

In your memo I would like to see as a minimum concise history of the DMSO problem, a summary of the toxicological and chemical/residue characteristics, and your assessments as to whether the RD position as stated in the December 10 letter from Mountfort should be supported or denied.

In presenting your endorsement or denial of the RD position, you should of course include your assessments of the potential impact on the public health by going one way or another. In addition your assessments should also speak to the potential of the compound to significantly potentiate the bioeffects of actives, and your recommendations for dealing with that potential.

for BC
JAMES M. CONLON
Acting Director,
Hazard Evaluation Division

JCONLON:bc:8/29/78

CONCURRENCES

SYMBOL							
SURNAME							
DATE							

57



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

AUG 28 1978

OFFICE OF TOXIC SUBSTANCES

SUBJECT: Crown Zellerbach Pesticide Petition 4F1486 Requesting an
Exemption from the Requirement for a Tolerance for DMSO

TO: ☒ Director, Hazard Evaluation Division TS-769
Director, Registration Division TS-767

FROM: Deputy Assistant Administrator
for Pesticide Programs TS-766

We have received a letter from Congressman Mike McCormack on behalf of Crown Zellerbach concerning their pending petition to exempt DMSO from the requirement of a tolerance. We have told them that because of DMSO's unique penetrating characteristics and the possibility that it enhances the penetration of the pesticide dissolved in it as well, they will have to petition for finite tolerances for each individual DMSO/pesticide/crop combination. Crown Zellerbach thinks it more rational to exempt DMSO itself as an inert and to require individual registrants of particular DMSO/pesticide products to submit necessary data on the possibility that DMSO in the formulation will result in increased residues of the pesticide on a given crop. In addition, a December 10, 1978, letter from Dick Mountfort has raised the issue of potentiation between DMSO and other chemicals. A copy of this letter is attached.

After considering the special problems presented by the DMSO petition, I have decided that Registration Division should give the petition file and all pertinent data available to Hazard Evaluation Division for a full review of the problem. I will expect a joint recommendation on the appropriate way to deal with DMSO by September 22, 1978. I have written to Congressman McCormack to this effect and will need to get back to him by the end of September. For your information I have attached copies of his letter and my response.

Edwin L. Johnson

Attachments

Rec'd Criteria and Evaluation

100-1070

12/10/76
12 DEC 1976

Pesticide Petition 4F1486

Mr. J. A. Chapman
Crown Zellerbach Corp.
Camas Washington
98607

Dear Mr. Chapman:

We are unable to act favorably on your request to expand the present exemption for dimethyl sulfoxide to include use as a solvent or cosolvent within 1 day of harvest. The question of potentiation between DMSO and other chemicals precludes further exemption. We believe that tolerance proposals for DMSO would be necessary to support each combination; ie. DMSO + parathion in wheat. Sufficient information would be required to support the proposals for DMSO and to show that established tolerances for the individual pesticide would not be exceeded.

Sincerely,

Richard F. Mountfort *RFM*
Product Manager (23) *12/10/76*
Fungicide-Herbicide Branch
Registration Division (WH-567)



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF TOXIC SUBSTANCES

Honorable Mike McCormack
House of Representatives
Washington, D. C. 20515

Dear Mr. McCormack:

Thank you for your letter of August 8, 1978, on behalf of Mr. J. A. Chapman, General Manager of the Chemical Products Division of Crown Zellerbach. Crown Zellerbach has had a pesticide petition (4F1486) pending before the Agency which requests an exemption from the requirement of a tolerance or legal residue level for dimethyl sulfoxide (DMSO). Recently Mr. Chapman noted that the Agency has exempted a number of pesticidally inert ingredients from the tolerance requirement without similarly granting a tolerance exemption for DMSO. He feels the Agency is not reviewing the Crown Zellerbach petition by the same standards we have used for these other inert ingredients.

Let me first explain that EPA regulates pesticide products directly under the provisions of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). It also establishes tolerances or exemptions from tolerances for residues of chemicals remaining on crops treated with pesticide products under the authority of the Federal Food, Drug, and Cosmetic Act (FFDCA). A tolerance or tolerance exemption must be established for any pesticide and any inert ingredient of a pesticide formulation intended for use on a food or feed crop. Crops bearing residues of pesticides or inert ingredients lacking established tolerances or exemptions are considered adulterated and may be subject to seizure by the Food and Drug Administration.

The Crown Zellerbach petition requesting an exemption for DMSO has presented us some particular problems not shared by the exempted inerts listed in the July 11, 1978, Federal Register notice enclosed by Mr. Chapman. Specifically, DMSO has unique solvent characteristics, allowing it to penetrate cell tissues and thus possibly enhancing penetration of the pesticide dissolved in it. Enhanced penetration of the pesticide could result in residues exceeding tolerances established for the pesticide itself and thus present a possible health hazard from consumption of crops bearing the increased residues. These issues must be resolved before a tolerance exemption could be granted.

-2-

Given the nature of DMSO, we have told Crown Zellerbach that it would be necessary for them to submit petitions with supporting data for the establishment of finite tolerances for each combination of DMSO and particular pesticide on a given crop in order to assure that enhanced penetration of pesticide residues will not present undue risks. Crown Zellerbach feels that it would be more reasonable to deal with this problem by exempting DMSO itself from the tolerance requirement and by requiring those pesticide producers who wish to register pesticide products formulated with DMSO under the provisions of the FIFRA to submit data on the enhanced penetration of residues of their particular product.

Because of the unique problems associated with exempting DMSO from the tolerance requirement, I have referred the petition to our Hazard Evaluation Division for a full review and reconsideration and have asked them to make a recommendation to me within a month. After I have received the recommendation, I will be in touch with you again to discuss our conclusions about the most appropriate way to satisfy the tolerance requirements of the FFDCA in the case of DMSO.

I appreciate Mr. Chapman's concern that the Agency handle the Crown Zellerbach petition in a reasonable and timely manner and hope you will reassure him of our efforts to resolve this issue promptly. In the meantime, if I may be of further service, please let me know.

Sincerely yours,

Edwin L. Johnson
Deputy Assistant Administrator
for Pesticide Programs

TSPX:ALINDSAY:acl:X58020:8/23/78 AL-5351
cc: TS(2) AL Region 10w/inc. Dave Ritter TS-769
Dick Mountfort TS-767
Doug Campt TS-767 w/inc. for ACTION
Mike Conlon TS-769 w/inc. for ACTION✓

MIKE MCCORMACK
4TH DISTRICT, WASHINGTON

COMMITTEES:
PUBLIC WORKS AND
TRANSPORTATION
SCIENCE AND TECHNOLOGY
CHAIRMAN
SUBCOMMITTEE ON ADVANCED ENERGY
TECHNOLOGIES AND CONSERVATION
AD HOC COMMITTEE ON ENERGY

Congress of the United States
House of Representatives
Washington, D.C. 20515

August 8, 1978

WASHINGTON OFFICE:
1202 LONGWORTH HOUSE OFFICE BUILDING
(202) 225-3816

DISTRICT OFFICES:
FEDERAL BUILDING
RICHLAND, WASHINGTON 99352
(509) 942-7273

305 NORTH 3RD STREET, SUITE 4
YAKIMA, WASHINGTON 98901
(509) 248-0103

FEDERAL BUILDING, 500 12TH
VANCOUVER, WASHINGTON 98660
(206) 696-4041, EXT. 256-7

FEDERAL BUILDING
WENATCHEE, WASHINGTON 98801
(509) 663-2214

Mr. Douglas M. Costle
Administrator
Environmental Protection Agency
Waterside Mall
401 "M" Street, S. W.
Washington, D. C. 20460


Dear Mr. Costle:

Enclosed is a copy of a letter sent to the
Office of Pesticide Programs, Environmental
Protection Agency, which describes an apparent
inconsistency in policy with regard to current
proposed rules, and dimethyl sulfoxide.

I would appreciate your comments on the points
raised by Mr. Chapman of Crown Zellerbach in
his letter.

Best wishes.

Sincerely,



Mike McCormack
Member of Congress

dcs

Enclosure

OTS-OAP

cc: [unclear] (over [unclear])

Mr. Sellwood says



CrownZellerbach

Chemical Products Division

1978

July 31, 1978

CERTIFIED MAIL -
RETURN RECEIPT REQUESTED

Federal Register Section
Technical Services Division (WH 569)
Office of Pesticide Programs
Environmental Protection Agency
Room 401 East Tower
401 M Street SW
Washington, D.C. 20460

Gentlemen:

Reference: Federal Register Vol. 43, No. 133 (6560-01)

The above reference proposes certain additional inert ingredients (or occasionally active ingredients) in pesticide formulations be exempted from tolerance requirements. The proposal lists various inert ingredients and concludes that the substances if used with good agricultural practices are useful and do not pose a hazard to the environment.

Approval of many of the proposed substances were based on the fact that they were previously cleared as food additives or were naturally occurring substances. These bases are inconsistent with the correspondence between your Agency and Crown Zellerbach relative to Crown Zellerbach's request to remove certain limitations on use of dimethyl sulfoxide (DMSO) as a pesticide solvent (Pesticide Petition 4F1486). Since March, 1974, Crown Zellerbach has supplied data on residue studies, feeding studies and toxicology information in support of this petition. The conclusions by your Agency for not approving removal of the limitations were based on a concern that DMSO may potentiate pesticides and that it would be necessary to propose tolerances for specific combination of DMSO with pesticides on specific crops. See attached.

It is surprising that your Agency would propose amending 40 CFR Part 180, thereby expanding the limits of the substances listed in the referenced Federal Register in that no potentiation data on specific pesticide combinations on specific crops were apparently submitted. If no data were submitted, then it would appear that since the substances are naturally occurring or were approved for one use they would not potentiate other active ingredients under another method of use.

Environmental Protection Agency

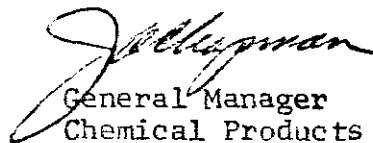
-2-

July 31, 1978

DMSO and its metabolites are naturally occurring in the environment (as evidenced by many studies, including one by your Agency) and DMSO is certainly less toxic and more volatile than most of the proposed substances.

We would appreciate your comments explaining the apparent inconsistency in the review process and data requirements.

Very truly yours,


General Manager
Chemical Products Division

J. A. CHAPMAN/hw

Attachment

cc: Mr. Sol Moser - w/a
Crown Zellerbach
Washington, D.C.

Sen. Henry M. Jackson - w/a
Sen. Warren G. Magnuson - w/a
Rep. Mike McCormack - w/a
Mr. Richard F. Mountfort, EPA

PROPOSED RULES

29809

[6560-01]

[40 CFR Part 180]

[OPP-300014; FRL 924-71]

TOLERANCES AND EXEMPTIONS FROM TOLERANCES FOR PESTICIDE CHEMICALS IN OR ON RAW AGRICULTURAL COMMODITIES

Proposed Exemption From Requirement of a Tolerance for Certain Inert Ingredients in Pesticide Formulations

AGENCY: Office of Pesticide Programs, Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: This notice proposes that certain additional inert ingredients (or occasionally active) ingredients in pesticide formulations be exempted from tolerance requirements. The proposal was submitted by various firms. This amendment to the regulations would permit the use of the exempted ingredients in pesticide formulations.

DATE: Comments must be received on or before August 10, 1978. Requests to refer this proposal to an Advisory

Committee must be received on or before August 10, 1978.

ADDRESS COMMENTS TO: Federal Register Section, Technical Services Division (WH-569), Office of Pesticide Programs, EPA, Room 401, East Tower, 401 M Street SW., Washington, D.C. 20460.

FOR FURTHER INFORMATION CONTACT:

Mr. David Ritter, Toxicology Branch, Registration Division (WH-567), Office of Pesticide Programs, EPA, 202-426-2680.

SUPPLEMENTARY INFORMATION:

At the request of several interested persons, the Administrator is proposing to amend 40 CFR 180.1001 by exempting certain additional pesticide chemicals which are inert (or occasionally active) ingredients in pesticide formulations from tolerance requirements.

Inert ingredients are all ingredients which are not active ingredients as defined in 40 CFR 162.3(c), and includes,

but is not limited to the following types of ingredients (except when they have pesticidal efficacy of their own):

Solvents such as water; baits such as sugar, starches, and meat scraps; dust carriers such as talc and clay; fillers; wetting and spreading agents; propellants in aerosol dispensers; and emulsifiers. The term inert is not intended to imply nontoxicity; the ingredient may or may not be chemically active.

The preambles to proposed rulemaking documents of this nature include the common or chemical name of the substance under consideration, the name and address of the firm making the request for the exemption, and the toxicological and other scientific bases used in arriving at a conclusion of safety in support of the exemption.

The amendment to 40 CFR Part 180 which is adding § 180.1040 pertains to ethylene glycol, a specific inert ingredient which is associated with a restricted use pattern. The basis for that restriction is that there would be no reasonable expectation of residues in the raw agricultural commodity. This

Inert ingredient	Firm	Bases for approval
n-Alkyl(C ₁ -C ₁₂) amine acetate	Armak Co., 8401 West 47th St., McCook, Ill. 60525.	Previously cleared under 21 CFR 172.710. 90-day dog and rat feeding studies.
N,N-Bis(2-hydroxyethyl) alkylamines	do	Parent group previously cleared under 40 CFR 180.1001(d). 90-day dog and rat feeding studies.
N,N-Bis(2-omega-hydroxypolyoxyethylene) ethyl alkylamine.	do	Parent compound previously cleared under 40 CFR 180.1001(d). No additional toxicologically significant exposure is expected from the proposed use.
Copper naphthenate	American Cyanamid Co., Princeton, N.J. 08540.	No reasonable expectation of residues on the raw agricultural commodities under applicable use restrictions.
Copper salts of neodecanoic acid and 2-ethyl hexanoic acid.	do	Copper salts previously cleared under 21 CFR as food additives and 40 CFR 180.1001(b)(1). Copper is an essential nutrient. Tolerance of 1 ppm previously established for neodecanoic acid on cottonseed based on dog and rat studies ethyl hexanoic acid previously cleared under 21 CFR 172.515 as a synthetic flavoring and under 40 CFR 180.1001(d) as its alcohol form.
Corn syrup	Clinton Corn Processing Co., Clinton, Iowa 52732.	Human dietary constituent.
D and C green No. 6	Burroughs Wellcome Co., Research Triangle Park, Durham, N.C. 27709.	Previously cleared under 40 CFR 180.1001(d). No reasonable expectation of residues in eggs, meat, or milk.
D and C red No. 17	do	Do.
D and C violet No. 2	do	Do.
Dialkyl(C ₁ -C ₁₂) dimethyl ammonium chloride, the dialkyl(C ₁ -C ₁₂) derived from tallow.	Armak Co., 8401 West 47th St., McCook, Ill. 60525.	Previously cleared under 21 CFR 178.1010 in sanitizing solutions contacting food and 172.712 in sugar solids. Tallow fatty acids are natural body constituents.
Douglas-fir bark, ground	Weyerhaeuser Co., 505 North Pearl St., Centralia, Wash. 98531.	Indigestible and harmless naturally occurring substance.
FD and C blue No. 1	Burroughs Wellcome Co., Research Triangle Park, Durham, N.C. 27709.	Previously cleared under 40 CFR 180.1001(e). No reasonable expectation of residues in eggs, meat, or milk.
Glycerol mono-, di-, and triacetate	Armak Co., 8401 West 47th St., McCook, Ill. 60525.	Naturally occurring body substances.
α-Pinene	Hercules, Inc., Wilmington, Del. 19899.	GRAS under 21 CFR 172.515 as synthetic flavoring.
Polyoxyethylene (5) sorbitan monooleate	ICI United States, Inc., Wilmington, Del. 19897.	Previously cleared under 21 CFR as a direct human food additive
n-Propanol	do	Previously cleared under 21 CFR 172.515 as a synthetic flavoring.
Styrene-maleic anhydride copolymer	Arco Chemical Co., 1500 Market St., Philadelphia, Pa. 19101.	Styrene component previously cleared under 21 CFR 172.515 as a synthetic flavoring agent. Long-term toxicity studies for maleic anhydride component which is cleared under 40 CFR 180.1001(d).
Tartrazine	Burroughs Wellcome Co., Research Triangle Park, Durham, N.C. 27709.	Previously cleared under 40 CFR 180.1001(d). No reasonable expectation of residues in eggs, meat, or milk.

29810

PROPOSED RULES

inert cannot be used in any other manner except as specified in the regulation and as determined in a specific product registered by the Agency in accordance with the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended (86 Stat. 973, 89 Stat. 751, 7 U.S.C. 136(a) et seq.).

Based on the above information, available data on the chemistry of these substances, and a review of their use, it has been found that, when used in accordance with good agricultural practice, these substances are useful and do not pose a hazard to the environment. It is concluded, therefore, that the proposed amendments to 40 CFR Part 180 will protect the public health, and it is proposed that the amendments be established as set forth below.

Any person who has registered, or submitted an application for the registration of a pesticide under FIFRA which contains any of the ingredients listed herein, may request, on or before August 10, 1978, that this proposal be referred to an advisory committee in accordance with section 408(e) of the Federal Food, Drug, and Cosmetic Act.

Interested persons are invited to submit written comments on the proposed regulation. The comments must bear a notation indicating both the subject matter and the OPP document control number "OPP-300014". All written comments filed in response to this notice will be available for public inspection in the office of the Federal Register section from 8:30 a.m. to 4 p.m. Monday through Friday.

Dated: May 19, 1978.

DOUGLAS D. CAMPT,
Acting Director,
Registration Division.

AUTHORITY: Sec. 408(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 346a(e)).

It is proposed that Part 180, Subpart D, be amended by (1) deleting the items "*N,N*-Bis(2-[omega-hydroxypoly(oxyethylene)] ethyl) alkyl amines; * * *", "*N,N*-Bis(2-omega-hydroxypoly(oxyethylene)] ethyl) alkyl amines; * * *", and "*N,N*-Bis(2-hydroxyethyl) alkylamine, where the alkyl groups (C₁-C₁₈) * * *" from the table in section 180.1001(d); (2) alphabetically inserting new items in the tables in section 180.1001 (c), (d), and (e); and (3) adding the new section 180.1040, as follows:

§ 180.1001 Exemptions from the requirement of a tolerance.

(c) * * *

Inert ingredients	Limits	Uses
Glycerol mono-, di-, and triacetate.....		Solvent, cosolvent.
n-Propanol.....		Solvent, cosolvent.

(d) * * *

Inert ingredients	Limits	Uses
n-Alkyl(C ₁ -C ₁₈)amine acetate.....		Surfactants, related adjuvants of surfactants.
<i>N,N</i> -Bis(2-hydroxyethyl) alkylamine, where the alkyl groups (C ₁ -C ₁₈) are derived from coconut, cottonseed, soya, or tallow acids.		Surfactants, related adjuvants of surfactants.
<i>N,N</i> -Bis 2-(omega-hydroxypolyoxyethylene) ethyl alkylamine; the reaction product of 1 mole <i>N,N</i> -Bis(2-hydroxyethyl) alkylamine and 2-60 moles of poly(oxyethylene) alkylamine, where the alkyl group (C ₁ -C ₁₈) is derived from coconut, cottonseed, soya, or tallow acids.		Do.
Copper naphthenate.....	Not more than 2.5 pct of formulation; application limited to before edible portions of plants begin to form.	Mercaptan scavenger in technical pesticide.
Copper salts of neodecanoic acid and 2-ethyl hexanoic acid.....	Not more than 1 pct of formulation; application limited to before edible portions of plants begin to form.	Do.
Di-alkyl(C ₁ -C ₁₈) dimethyl ammonium chloride, (C ₁ -C ₁₈) group from tallow.....		Surfactants, related adjuvants of surfactants.
Douglas-fir bark, ground.....		Solid diluent, carrier.

PROPOSED RULES

29811

(d) * * *		
Inert ingredients	Limits	Uses
α -Pinene	Not more than 2 pct of formulation by weight.	Stabilizer.
Polyoxyethylene (5) sorbitan monooleate		Surfactants, related adjuvants of surfactants.
Styrene-maleic anhydride copolymer	For preemergence use only.	Suspending or dispersing agent.
(e) * * *		
Inert ingredients	Limits	Uses
Corn syrup		Sticker, attractant.
D and C green No. 6		Dye, coloring agent.
D and C red No. 17		Do.
D and C violet No. 2		Do.
FD and C blue No. 1		Dye, coloring agent.
α -Pinene	Not more than 2 pct of formulation by weight.	Stabilizer.
Tartrazine		Dye, coloring agent.

2. Part 180, Subpart D, is amended by adding the new § 180.1040 to read as follows:

§ 180.1040 Ethylene glycol; exemption from the requirement of a tolerance.

Ethylene glycol as a component of pesticide formulations is exempt from the requirement of a tolerance when used in foliar applications to peanut plants.

[FR Doc. 78-18812 Filed 7-10-78; 8:45 am]

[4310-84]

DEPARTMENT OF THE INTERIOR

Bureau of Land Management

[43 CFR Parts 3200, 3220]

GEOHERMAL RESOURCES LEASING; GENERAL COMPETITIVE LEASES

Miscellaneous Amendments

AGENCY: Bureau of Land Management, Interior.

ACTION: Notice of comment period extension.

SUMMARY: Proposed rulemaking regarding the competitive leasing of geothermal resources was published on pages 20826 and 20827 of the FEDERAL REGISTER of May 15, 1978. Public comments were invited through July 14, 1978. This notice extends that comment period to August 15, 1978, to provide for more complete analysis of the rulemaking by interested persons and agencies.

DATE: Comment by August 15, 1978.

ADDRESS: Send comments to: Director (210), Bureau of Land Management, 1800 C Street NW., Washington, D.C. 20240. Comments will be available for public review at the above address from 7:45 a.m. to 4:15 p.m. on regular work days.

FOR FURTHER INFORMATION CONTACT:

Billy R. Templeton at the above address or telephone 202-343-8735.

ARNOLD E. PETTY,
Acting Associate Director.

JULY 6, 1978.

[FR Doc. 78-19048 Filed 7-10-78; 8:45 am]

[4910-60]

DEPARTMENT OF TRANSPORTATION

Materials Transportation Bureau

[49 CFR Part 191]

[Docket No. OPS-49; Notice 2]

TRANSPORTATION OF NATURAL AND OTHER GAS BY PIPELINE

Leak Reporting Requirements; Extension of Comments Period

AGENCY: Materials Transportation Bureau (MTB).

ACTION: Extension of comment period.

SUMMARY: This notice extends the period for comment to the notice published June 5, 1978 (43 FR 24478), from July 10, 1978, until August 10, 1978.

DATE: Comments must be received on or before August 10, 1978.

ADDRESS: Comments should identify the docket and notice number and be



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

Pesticide Petition 4F1486

15 FEB 1978

Mr. J. A. Chapman
Crown Zellerbach
Chemical Products Division
Camas, Washington 98607

Dear Mr. Chapman:

We are reluctant to pre-judge test results before a program is completed. The proposed protocol drawn up by Rhoads Scientific Company, however, will not suffice to permit expansion of the present exemption for dimethyl sulfoxide. As we have stated, it will be necessary to propose tolerances for specific combinations of the solvent with pesticides on specific crops. We do not believe that sampling, no matter how representative, of pesticides and crops, will be adequate for us to conclude that dimethyl sulfoxide should be further exempted. We are concerned both with applicator safety and effect on residue levels in the crop when DMSO is combined with toxicants.

Sincerely,

Richard F Mountfort

Richard F. Mountfort
Product Manager (23)
Fungicide-Herbicide Branch
Registration Division (WH-567)

RECEIVED
FEB 21 1978
CH. P.D.

**CrownZellerbach**

Chemical Products Division

February 7, 1978

CERTIFIED MAIL -
RETURN RECEIPT REQUESTED

Fungicide-Herbicide Branch
Registration Division (WH-567)
United States Environmental Protection Agency
Washington, D.C. 20460

Attn: Mr. Richard F. Mountfort
Product Manager (23)

Gentlemen:

Subject: Pesticide Petition No. 4F1486

In your letter of October 21, 1977 and previous correspondence, you indicated the agency needs additional information to assess potential hazards involved when using dimethyl sulfoxide as a pesticide solvent. Specifically, the question is: would the use of this solvent potentiate the active ingredient such that established tolerances for the individual pesticide would be exceeded?

Obviously, it would be impossible to develop information concerning every possible combination of pesticides, solvents and crops. However, we have contracted with a consulting firm, specializing in agrichemical research, to develop a protocol for a study that would provide meaningful information for our petition.

If you will note from the attached, the consultant proposes a comparative study of determining residues of pesticides selected from five structural classes on crops selected from five commodity groups. A residue comparison would be made between formulations involving the solvent, tetrahydrofurfuryl alcohol, and the solvent dimethyl sulfoxide. Tetrahydrofurfuryl alcohol was chosen because it is exempt from tolerance when applied to growing crops or raw agricultural commodities after harvest and it has properties similar to those of dimethyl sulfoxide (polar, water soluble, low volatility).

We would appreciate your study of the protocol. Before proceeding, we would like an indication from your agency whether results of this study, in addition to that we have provided over the past seven years, would provide sufficient information to answer the question of the potential hazard of dimethyl sulfoxide use on food crops.

Very truly yours,



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

Pesticide Petition 4F1486

21 OCT 1977

Mr. J. A. Chapman
Crown Zellerbach Corp.
Camas, Washington
98607

Dear Mr. Chapman:

We have your letter of July 8, 1977 and do not agree that the proposed expansion of the present exemption for the solvent dimethyl sulfoxide should be granted. We are prepared to consider proposed tolerances for specific combinations of the solvent with pesticides on specific crops. An adequate evaluation of the potential hazards from use of dimethyl sulfoxide must include such proposals and sufficient data on each combination to describe the actual hazard and support the tolerance level for DMSO and the pesticide(s) involved. This action supports our responsibility under Section 3 of the Act, as amended, to register a pesticide if "it will perform its intended function without unreasonable adverse effects on the environment" and "when used in accordance with widespread and commonly recognized practice it will not generally cause unreasonable adverse effects on the environment" [Sections 3(c)(5)(C) and (D) of the Act]. Applicants for individual formulations will be required to provide sufficient information to support their proposed registrations. This does not, however, relieve you as proponent of this exemption request, from documenting your proposal sufficiently for us to assess the potential hazards involved. This you have not done and we feel you cannot do unless you propose and provide adequate support for finite tolerances(s). Our review of inert ingredients in pesticide formulations is being strengthened. Questions and decisions presently applied to DMSO may be required of other inerts. It is not sufficient, however, to quote prior exemptions for other solvents as a substitute for hazard assessment for dimethyl sulfoxide.

RECEIVED
NOV 1 1977
CH. P. D.

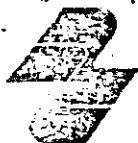
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Your comments on the applicability of provisions of the Act to changes in a pesticide formulation are noted. Unauthorized changes in a registered pesticide formulation constitute a violation [Section 12(a)(1)(C) of the Act].

Sincerely,



Richard F. Mountfort
Product Manager (23)
Fungicide-Herbicide Branch
Registration Division (WH-567)



CrownZellerbach
Chemical Products Division

July 8, 1977

Fungicide-Herbicide Branch
Registration Division (WH-567)
United States Environmental Protection Agency
Washington, D. C. 20460

Attn: Mr. Richard F. Mountfort
Product Manager (23)

J.A.C.

Gentlemen:

Subject: Pesticide Petition No. 4F1486
Your letters of December 10, 1976 and April 8, 1977

We assume from your letters your reluctance to act favorably on the subject petition stems from the following premises:

1. Producers of pesticide formulations may change the inert ingredients of the formulation without notifying the EPA, and if so, could produce a mixture containing solvents or adjuvants that would increase penetration and/or residues of the contained active ingredient.
2. DMSO has the ability of penetrating cell tissues and can enhance penetration of dissolved materials, while other solvents or adjuvants having tolerance exemption under 40 CFR 180.1001 do not.

If the first premise is correct, then we believe such action would be in conflict with FIFRA Pub. Law 92-516, Section 3. If a manufacturer of a final formulation changes the composition of the formulation and does not show evidence that satisfactory pesticide residues would result or that a hazard to humans and animals would not exist when the formulation is applied according to the label, it is our interpretation that violation of the public law would exist. Under FIFRA, manufacturers cannot change systems, incorporating even other exempted solvents, without your agency's approval. Such approvals would occur only after EPA's analysis of both the toxicological data of the new formulation (not only the active ingredient per se) and the concentration of the pesticide contained in the crop tissue. This interpretation of the existing laws has been reaffirmed through discussions with pesticide manufacturers.

The second premise, if it exists with your agency, is a common misunderstanding of the properties of DMSO. The fact that your conclusions were not supported by any scientific data points again to a judgment based on

Mr. Richard F. Mountf t

-2-

Ju 8, 1977

hearsay and rumors. DMSO does penetrate cell tissue, however, leading toxicologists have shown that most liquids, including water, penetrate tissue. The fact that all organic solvents exhibit acute dermal toxicity indicates permeation and absorption. The interesting aspect of DMSO is that it has a very low dermal toxicity (the lowest reported value of any existing organic solvent). Because of this low toxicity, the medical community in the early 1960's became interested in the possibility of using topical solutions of DMSO to carry drugs across skin membranes. There was considerable activity with this for a time, however, continual reported failures of enhanced penetration of the active ingredients brought this research to a halt throughout the country. It was found in most instances that the DMSO penetrated the skin but the drug product was left behind in the epidermis. In instances where some penetration was noted, the increase over other adjuvants was not significant. No commercial use of DMSO as a transport agent for a pharmaceutical exists.

The same activity occurred in the pesticide field. Knowing DMSO has low phytotoxicity, many leading companies conducted studies to determine the effectiveness of DMSO as a pesticide carrier, particularly in foliar applications. Not one found sufficient evidence of enhanced effects to warrant continued studies.

As to the concern that DMSO has greater ability to carry materials through living membranes than solvents and adjuvants currently having tolerance exemptions without limitations, much published literature contradicts such a claim. Ethanol and water are reported to be as effective in increasing skin permeability of phenol as DMSO (1). Xylene is reported to accelerate the skin penetration of drugs (2). Skin absorption of the steroid, estriol was found to be greater in corn oil than DMSO (3). Malathion, lindane and unbelliferone phosphonate dissolved in DMSO were less toxic to insects than when dissolved in acetone (4). Penetration of dodecyl sulfate 35^S through whole human abdominal skin was greater in a water solution than from a DMSO solution (5). In vitro absorption of the strongly polar insecticides, trichlorfon and dimethoate, through cattle skin was found to increase as polarity of the solvent (various alcohols) decreased and absorption of weakly polar insecticide butonate, exhibited the reverse result. Absorption of all three insecticides was greatly increased by addition of surfactants but addition of DMSO increased only the butonate resorption (6).

Control of spider mite by injection of dimethoate in cherry trees was found to be similarly effective when the pesticide was dissolved in ethanol, tetrahydrofuran, DMSO or as a water emulsion (7). Control of blossom blight on Bartlett pear was less with a streptomycin-water-DMSO foliar spray than with a straight streptomycin-water spray (8). Addition of X-77, DMSO, endothal and amitrole-T to paraquat solutions showed similar results in necrosis rate of hibiscus leaves (9).

Mr. Richard F. Mountfort

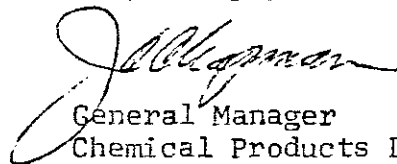
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July 8, 1977

We feel there is sufficient evidence to show that DMSO cannot be cited as being more of a potentiator than any of the tolerance exempt solvents and adjuvants under 40 CFR, 180.1001 (c) and (d). Further, that if DMSO is used in a formulation developed by a pesticide manufacturer, full toxicological and residue data must be provided to your agency as required under FIFRA and determination as to the formulation's safety can be made at that time.

Therefore, considering these aforementioned safeguards, in addition to the previously submitted data, we request approval of Petition No. 4Fl486.

Very truly yours,



General Manager
Chemical Products Division

J. A. CHAPMAN/hw

cc: Mr. John Ritch
Dr. Martin Rogoff

- (1) Roberts, et al, Univ. Sydney, J. Pharm. Pharmacol, 1975, 27(8) 599-605 (England)
- (2) Creasey, et al, Brit. J. Dermatol, 1971, 85(4), 368-80 (England)
- (3) Jones, et al, Poultry Science, 1967, 46(1), 249-250.
- (4) Enriquez, et al, Bol. Real Soc. Espan. Hist. Natur., Secc. Biol., 1969, 67(1-2), 71-4, C.A. 73, 86878j.
- (5) Embery et al, Brit. J. Dermatol. Suppl. 1969, 81(4), 63-8 (England)
- (6) Dedek, et al, Arch. Exp. Veterinaarmed. 1975, 29(6), 857-68 (Germany)
- (7) Harries, F.H., J. of Economic Entomology, 1965, 58(4), 631-634.
- (8) Zehr, E. I., Phytopathology, 1968, 58, 1624-1629.
- (9) Bovey, R. W., Miller, F.R., Weed Res., 1968, 8, 128-135

cc: B. A. Bailey

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

8 APR 1977

Crown Zellerbach
Attention: J. A. Chapman
Chemical Products Division
Camas, Washington 98607

Gentlemen:

Subject: PESTICIDE PETITION NO. 4F1486
Your letters of January 3 and March 18, 1977

We do not believe that you have submitted sufficient information to permit further exemption for the solvent DMSO or to allay concern over potentiation. The solvent and a broad range of toxicants could be combined as a result of further exemption. You have mentioned oral toxicity studies with five pesticides but have presented no information on other routes of exposure. DMSO readily penetrates cell tissue, animal and plant, and can enhance penetration by other compounds. Your tolerance proposals should not only show that hazard is not increased in combination, but that established tolerances are not affected.

Sincerely,

Richard F. Mountfort
Richard F. Mountfort
Product Manager (23)
Fungicide-Herbicide Branch
Registration Division (WH-567)

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APR 14 1977

CH. P.D.

J.A.C.

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~~A. Bradley~~
fll → PP 4F1486

DMSO, PP# 4F1486, your memo 9/25/78

J. G. Cummings, Chief, Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

Acting Director, HED (TS-769)

Reply to your questions in the order presented:

1. It is not unusual to have solvents listed as active ingredients on insecticide labeling. However, RD has been unable to locate any record of DMSO as an active ingredient on product labeling.
2. It would be possible to issue a regulation controlling DMSO residues, based on its own toxicological significance and without regard to its effects on active ingredients. The tolerance would necessarily be tied to the agricultural practices employed.
3. It is likely that many solvents and adjuvants enhance penetration of active ingredients through plant and animal membranes. It therefore becomes a matter of degree with DMSO. The reputation of DMSO for this property may be traced to the publicity it received some years ago as a pharmaceutical agent and to the experience of laboratory workers in which it can be tasted in the mouth moments after skin contact.
4. For the reasons explained in the previous memo we believe tolerances could be established for DMSO as an inert.
5. Question 5 is not entirely clear to me. Presumably any formulations containing DMSO would be subject to review at time of registration, where evidence would be required as to whether residues of a.i. were extended, and whether the toxicity of the formulation to applicators was enhanced. RD would have to develop an SOP of this.
6. The Comptroller General report to the Congress (Dec. 1975) pointed out deficiencies in the Agency's procedure for clearing inerts. The Agency's response to the Congress (see attached news clip) included a statement that tolerances were required for inerts if residues remained on foods. To date, a tolerance has not been established for any inert.

The still unresolved issue of tolerances vs. exemptions for inerts is summarized in the attached memo 12/10/75 re epichlorohydrin.

J. G. Cummings

TS-769:RCB:JGCUMMINGS:sdb:x62610:rm108:WSME:10/2/78
cc: Ritter, Inerts (PF), JGC, RF

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: September 8, 1978

SUBJECT: PP #4F1486 -- Dimethyl Sulfoxide (DMSO), exemption
from the requirement of a tolerance.

FROM:

FROM: Adjuvants Toxicologist
TO: Toxicology Branch, HED (TS-769)

0.2 9/12/78

TO: Acting Director
Hazard Evaluation Division (TS-769)

THRU: Acting Deputy Chief
Toxicology Branch, HED (TS-769)

THRU: Acting Chief
Toxicology Branch, HED (TS-769)

This is in response to your "Note to" of 8/29/78 concerning resolution of the DMSO petition noted above.

DMSO Background

DMSO is a solvent that possesses several unusual properties, among these being the propensity to rapidly and massive penetrate the skin. Within seconds, the individual experiences a garlicky taste or presence in his mouth that has been described by some as unpleasant. This property quickly to cross the dermal barrier was exploited during the 60's as a means of administering drugs topically, the theory being that such rapid penetration of skin would perhaps be a means of carrying large amounts of therapeutic agents into the body, especially at sites where there were injuries, e.g., a strained muscle, carcinomas, etc. This has proven to be unfeasible, however, and attempts to administer most drugs per se dermally in DMSO have largely failed. For practical purposes DMSO does not enhance drug absorption across the skin to any significant degree, although much clinical work is still being conducted.

DMSO Mammalian Toxicity

The toxicity of DMSO in mammalian systems is very low

1. Monkey 18 mo. oral NEL = 3 gm/kg/day
2. Dog 8 mo. oral NEL = 5 gm/kg/day
3. Dog 6 mo. oral NEL = 2.5 gm/kg/day (w/lens changes at highest dose)
4. Swine 90 day dermal NEL = 8 ml/kg/day (w/lens changes)
5. Rat teratology negative at up to 12 gm/kg.

- 2 -

6. Rat oncogenesis negative at 50 ppm in drinking water
7. Comparative Pesticide Toxicity - DMSO used as a solvent did not material increase the oral LD₅₀ toxicity of thiram, dieldrin, parathion, carbaryl or MC-A-600 in female rats when compared to that of corn oil and water.
8. Clinical experience - only 1 of 43 patients treated with DMSO for up to 21 months dermally showed evidence of lens effect; this could have been due to pre-existing pathology.
9. Antigens dissolved in DMSO penetrate the skin of volunteers no deeper than the horny layer; the degree of penetration appears to depend on the molecular weight of the antigen.
10. DMSO is the carrier/solvent of choice in the Ames test for mutagenicity.

A large body of clinical experience indicates that DMSO enhances dermal absorption of some drugs and therapeutic agents; produces localized dermatitis; an occasional allergic reaction and halitosis.

The ADI in man is 150 mg/day based on the 18 month monkey NOEL of 5000 mg/kg/day and an 8 month dog study NOEL of 5000 mg/kg using a very conservative safety factor of 2000-fold.

While not at all exhaustive, the above outline demonstrates the extremely low toxicity of DMSO from oral and dermal exposure in mammals. For a more exhaustive treatment of the experience with DMSO please see ANNALS OF THE NEW YORK ACADEMY OF SCIENCES 141:1, pp. 1-671, 3/15/67, C.D. Leake, Ed. and Ann. N.Y. Acad. Sci., 243, 1/27/75, Jacob & Herschler, Eds.

Toxicology Branch Position

TOX/HED cannot support the 12/10/77 R. Mountfort letter to Crown Zellerbach (CZ, the petitioner) for the following reasons:

Require "potentiation" of Residues Studies

1. The petition is a request to exempt DMSO per se from the requirements of tolerance as an inert ingredient (solvent) pursuant to provisions of Sec. 408 and 409 of Federal Food, Drug and Cosmetic Act (FFDCA). Such exemptions for "inerts" are based on a finding of no hazard

- 3 -

when the material is used in accordance with good agricultural practice, i.e., when the label directions are followed [conditions of proposed use - sec. 409 (b) (1)].

In our review of 11/25/75, D. Ritter, we concluded that the proposed exemption was safe and would protect the public health. The Mountfort letter stipulates that additional data on various combinations of DMSO with active ingredients (AIs) "...are needed to show that existing tolerances (for actives) - parentheses mine - would not be exceeded...".

Our Comment

RCB and TOX agreed with CZ that the question of potentiation of residues could be handled at the time of registration of the new individual formulations. See the R. Bayak memo of conference, 1/23/75.

Our position is unchanged on this issue.

Our reasons for requiring potentiation data from the registrant rather than from CZ in connection with the proposed exemption are as follows:

1. It puts the burden of proof for safety and its attendant costs upon the registrant, where it more properly belongs;
2. It will provide additional toxicity data for the actual formulations per se;
3. It will make the registrant responsible for formally petitioning the Agency for a tolerance that needs to be raised.
4. To require CZ to provide residue data on various AI-DMSO combinations would seem to ignore two important considerations:
 - a. CZ is not in the formulating business and probably does not have the expertise nor the resources to conduct the extensive and costly studies needed. (We have not asked other prime solvents suppliers to do this in the past). Anything provided along these lines by CZ would of necessity be only speculative.

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- b. Formulators are not likely to divulge their formulations to CZ because of Trade Secret considerations.
- c. Formulators in any case will have to provide the data on their product at the time of registration regardless of whether CZ also provides data.

2. Tolerances for DMSO as an inert ingredient

TOX addressed this question in the 10/16/75 memo of D. Ritter. We concluded that tolerances were not appropriate, based on the extremely low level of mammalian toxicity. RCB essentially agreed with this position in their memo of 4/9/76, R. Hummel.

Our Comment

EPA has not established tolerances per se for adjuvant chemicals; rather, we have exempted such adjuvants from the requirement of a tolerance pursuant to provisions of 40 CFR 180.1001 and ff.

The procedures, criteria and considerations used by the Adjuvants Toxicologist in making recommendations for adjuvant or inert chemicals are summarized in the attached memorandum of 2/24/77 E. Ritter. These requirements are different in some respects from those used to qualify AIs for actual residues tolerances; this is due principally to policy and fiscal considerations.

TOX has made many recommendations to clear adjuvants including highly polar solvents, without requiring the massive amount of TOX data submitted in support of the present proposal. These include hydrofurfural alcohol, dipropylene glycol, etc. More often than not, such clearances were granted upon the receipt of a letter and appropriate application of the principles noted in the above cited memo.

On the basis of the comparative toxicities of these solvents themselves, it would appear that DMSO is not being treated fairly by requiring a tolerance without requiring one for the others.

RCB's position respecting tolerances for inerts as we understand it is as follows: TOX is saying in effect that any amount present on the rac is safe when an inert is exempted. A tolerance, on the other hand, is an indication that a residue above tolerance is not safe; hence, establishing a tolerance for an inert is more appropriate, especially if a limitation, such as a 24 hour PHI, is needed.

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This position appears to include a margin for at least some forms of misuse or other contamination.

TOX, on the other hand, holds the countervailing view:

A "Tolerance" is an effective means of controlling pesticide use and thereby protects the public health. A tolerance is not an index of actual exposure. As noted above for inerts, tolerances are established on the basis of conditions of proposed use. Accordingly, a tolerance (and by reference, an exemption) should not be established to cover a possible misuse. We believe that the whole reason for tolerances is to protect against misuse, with severe penalties (crop seizure by FDA) when it occurs and is detected. If applicators were to discover that they can apply, say, 2X or 3X and not get residues over the tolerance limit, then it seems to us that the potential for misuse in the field is greatly increased. [Sec. 409(c)(4)(A) requires that a food additive tolerance, and by reference, a pesticide or inert residue, shall not be set at a level higher than that needed to accomplish the intended effect].

Accordingly, TOX recommendations for clearance of inerts applies only to the extent that good agricultural practice is followed. In effect, we are saying that the exemption is safe and will protect the public health, if and only if the material has been applied in accordance with good agricultural practice. By law, any other mode of application could result in violative residues, subject to appropriate enforcement action.

Does the above mean that TOX considers that any residue resulting from misuse is unsafe? Normally not. That's why we apply safety factors to inerts, when the evidence seem to warrant it. As noted above, the safety factor for DMSO is 2000-fold based on a chronic feeding NCEL. Thus, any conceivable misuse or accidental exposure would be without hazard from a DMSO residue standpoint, and therefore, an exemption, not a tolerance, is appropriate.

A Brief Chronology of PP #4F1486, Exemption for DMSO

1. Petition filed 4/10/74, L. Zink.
2. TOX recommends favorably for exemption, 5/2/74, C. Williams,
3. RCB requests additional residue data 7/24/74, I. Beyak,
4. TOX concurs w/RCB re data; refers question of increased AIs; need for tolerances, 9/7/74, D. Ritter,

- 6 -

5. Memo of conference, CZ, TOX, RCB - AIs to be handled at registration, 1/23/75, R. Beyak.
6. CB requests additional residue data, 9/16/75, R. Hummel.
7. TOX now recommends exemption - safety OK, 10/16/75, Ritter.
8. Limitations increased by amendment, 11/16/75, R. Mountfort.
9. TOX OKs restriction increase, 11/25/75, E. Ritter.
10. RCB OKs " " , 4/6/76, R. Hummel.
11. RCB now requests tolerance, 7/20/76, R. Hummel.
12. CZ letter objecting to tolerances, 8/16/76, Chapman.
13. TOX comments re CZ objections - agrees with CZ, 10/19/76, D. Ritter.
14. RCB requires potentiation data due to PSC, 4/4/77, R. Hummel.
15. RD now needs data for each combination with AI; exemption precluded, 12/10/77, R. Mountfort.

Potential Impact on Public Health

1. Due to the demonstrated extremely low level of toxicity of DMSO we would expect no increase in risk to public health as a result of the proposed use, including an exemption.
2. The Pesticide Applicator could benefit from using DMSO to replace more acutely toxic solvents such as xylene, toluene, diesel oil, etc. Moreover, the applicator would have a built-in "signal" should he inadvertently splash some DMSO-bearing formulation on his skin - he would taste the DMSO within seconds of the accident and could take corrective measure very quickly. This would be advantageous in the case of very toxic materials such as the widely used parathion or aldicarb preparations.

Any potential for increased toxicity due to DMSO in combination with an AI will be assessed at the time of registration of the product.

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Recommendations for handling possible instances of DMSO potentiation

1. Assuming that all petitions, registrations and amendments upon receipt in OPP pass through an initial clearing and tracking unit, such as the old RET, we could:
 - a. Let the application be examined to determine whether DMSO is in the formulation. If not, track routinely.
 - b. If DMSO is present, RET will flag for comment to RCB as to adequacy of supporting data; whether supporting tolerances are needed. If not, return application with note to RET.
 - c. If additional or increased tolerances are needed, RCB informs RET or appropriate PM and requests tolerance petition, etc.

David L. Ritter

R/D Init: REngler 9/7/78

A. E. W. 9/7/78

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PP4F1486

DMSO, Crown Zellerbach petition 4F1486, (your note 8/29)

Chief, RCB

J. M. Conlon, Acting Director, HED (TS-769)

The records of this petition have been reviewed as requested. The salient points in the history of the DMSO petitions are summarized along with a statement of the unresolved issues and RCB recommendations.

Chrono

1. 7/28/70, PP# 1E1017 submitted by CZ proposed exemption for DMSO for use on all growing crops. Because of data deficiencies, proposal was reduced to pre-emergence treatments of corn and soybeans only. A regulation (180.1001(d)) exempting DMSO for this use issued.
2. 2/23/73, PP# 3E1364 submitted by CZ proposed that 180.1001(d) be amended to permit pre-emergence use on all crops. Regulation issued 8/16/73 granting amendment as proposed and is still in effect.
3. 3/29/74, PP# 4E1486 submitted by CZ proposed exemption for application DMSO to all growing crops with 24 hour pre-harvest restriction. Petition is presently in reject status. Chronology follows:

5/7/74, TOX recommends for exemption as proposed

7/24/74, Chemistry Branch recommends against - (inadequate information on nature of residues from foliar sprays).

7/29/74, Environ. Chem. recommends against (no PR 70-15 data)

8/2/74, Company informed petition denied

8/3/74, Petition amended

9/13/74, TOX finds that residues in fruits & vegetables (2 and 5 ppm) are toxicologically significant and recommends that tolerance be considered instead of exemption.

11/2/74, CZ informed petition denied on grounds of TOX, Residue, Chemistry, and Env. Chem. deficiencies.

5/16/75, Petition amended

9/16/75, Chemistry recommends against on residue data deficiencies and cites need for tolerance as per TOX recommendation of 9/13/74.

-2-

10/16/75, TOX recommends for exemption contingent on concurrence of Chemistry.

11/20/75, Petition amended to prohibit use on forage crops after emergence.

4/9/76, Chemistry concurs in TOX recommendation for exemption.

7/20/76, Chemistry suggests appropriate tolerance levels as per new RD policy on tolerance for inerts.

10/14/76, TOX replies point-by-point to CZ and finds exemption appropriate.

12/6/76, RD sends CB chemist to CZ labs to CZ labs to conduct method trial on assumption that tolerance is viable.

12/16/76, PM 23 informs petitioner that exemption denied and cites potentiation with other chemicals. Also informs that tolerance proposal necessary with each UNSO/a.i./crop combination.

1/5/77, Report method trial successful

4/4/77, Chemistry recommends appropriate tolerance levels for crops, eggs, meat, milk.

Subsequent to this there followed a series of correspondence exchanges between PM 23 and CZ which essentially reiterated the positions.

Statement of unresolved issues

1. Exemption vs. tolerance

As the chronology shows, there were several reversals of opinion within the science branches on this point. The first reversal was for scientific reasons. The second was because of new policy regarding regulation of residues of inerts which was under development in OPP at that time. It was prompted by a GAO report which was critical of the Agency's procedure for clearing inerts for use on food crops. The Agency replied in a letter to the Congress that tolerances would be set for inerts (where appropriate). IFISO (and another inert, epichlorohydrin) were appropriate prototypes. Without a detailed analysis of exemptions vs tolerances, the basic criteria are that (a) if the inert requires some use restriction, (e.g., a PHI), in order to reduce residues to a level acceptable to TOX, it should not receive an exemption; (b) if residues could occur through gross misuse, accident, or any reasonable means at some level which could cause injury, it should not receive an exemption. (See also SAS Study Group on Tolerances draft working paper).

-3-

RCB recommendation: The proposed foliar uses of DMSO will produce real and persistent residues in food crops and trace levels in meat/milk/eggs. The exposure to humans should be controlled by tolerances and not an exemption. There are adequate residue data available to support the tolerance recommended in Dr. Hummel's evaluation of 4/4/77.

2. Requirement for separate tolerance petition for each DMSO/a.i./crop combination.

The petition record does not show how this requirement arose. It was not from the Science Branches. The letter of 10 Dec. 76 from PM 23 to CZ informing of this requirement possibly was based on discussions between PM 23 and the Pesticide Science Officer, RD. The Science Branches (TOX and CB) stated in their review that possible effects of DMSO on residue levels of a.i. could be handled at time of registration.

Recommendation: Assuming that DMSO tolerances may be set, this "potentiation" of a.i. could be controlled through the registration process, providing that a SOP is set up for RD review staff to do this.

Additional Comment

1. The term "potentiation" has been used in the PM/CZ correspondence to denote an extending effect by DMSO on residues of a.i. This should not be confused with the normal meaning of potentiation in pesticide terminology, which is that the total toxic effects of two chemicals administered together is greater than the sum of the effects when administered separately.
2. RD should clarify whether PR Notice 323, 6/6/68 is still operative. This PR Notice limited DMSO to 1% of any formulation, and required declaration as an active ingredient, among other things.
3. Mr. Ritter (TOX) is preparing a memo summarizing the TOX recommendations. It may be necessary to reconcile still differing opinions on exemption vs. tolerance.

J. G. Cummings
Chief, Residue Chemistry Branch
Hazard Evaluation Division

TS-769:RCB:JGCUMMINGS:sdb:X62610:RM108:9/7/73
cc: TOX(2), L. Dale, D. Ritter, PP# 4F1486, RF, Hummel

AUG 29 1978

NOTE TO: Lamar Dale

✓ Joe Cummings

SUBJECT: Crown Zellerbach Petition 4F1486 Requesting an Exemption
from the Requirement for a Tolerance for DMSO

Attached is a copy of subject memo which I received from Ed Johnson in which he directs that we conduct a full review of the DMSO problem, with joint RD/HED recommendations in his hands by September 22. As a first step toward providing that recommendation, I would like you to review the appropriate records and data and provide me with a joint recommendation by September 15.

In your memo I would like to see as a minimum concise history of the DMSO problem, a summary of the toxicological and chemical/residue characteristics, and your assessments as to whether the RD position as stated in the December 10 letter from Mountfort should be supported or denied.

In presenting your endorsement or denial of the RD position, you should of course include your assessments of the potential impact on the public health by going one way or another. In addition your assessments should also speak to the potential of the compound to significantly potentiate the bioeffects of actives, and your recommendations for dealing with that potential.

Jo Brenda Coward
JAMES H. CONLON
Acting Director,
Hazard Evaluation Division
CONLON:BC:8/29/78



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

AUG 28 1978

OFFICE OF TOXIC SUBSTANCES

SUBJECT: Crown Zellerbach Pesticide Petition 4F1486 Requesting an
Exemption from the Requirement for a Tolerance for DMSO

TO: ✓ Director, Hazard Evaluation Division TS-769
Director, Registration Division TS-767

FROM: Deputy Assistant Administrator
for Pesticide Programs TS-766

We have received a letter from Congressman Mike McCormack on behalf of Crown Zellerbach concerning their pending petition to exempt DMSO from the requirement of a tolerance. We have told them that because of DMSO's unique penetrating characteristics and the possibility that it enhances the penetration of the pesticide dissolved in it as well, they will have to petition for finite tolerances for each individual DMSO/pesticide/crop combination. Crown Zellerbach thinks it more rational to exempt DMSO itself as an inert and to require individual registrants of particular DMSO/pesticide products to submit necessary data on the possibility that DMSO in the formulation will result in increased residues of the pesticide on a given crop. In addition, a December 10, 1978, letter from Dick Mountfort has raised the issue of potentiation between DMSO and other chemicals. A copy of this letter is attached.

After considering the special problems presented by the DMSO petition, I have decided that Registration Division should give the petition file and all pertinent data available to Hazard Evaluation Division for a full review of the problem. I will expect a joint recommendation on the appropriate way to deal with DMSO by September 22, 1978. I have written to Congressman McCormack to this effect and will need to get back to him by the end of September. For your information I have attached copies of his letter and my response.

Edwin L. Johnson

Attachments

Rec'd Criteria and Evaluation

AUG 30 1978

12/10/76
12 DEC 1976

Pesticide Petition 4F1486

Mr. J. A. Chapman
Crown Zellerback Corp.
Camas Washington
98607

Dear Mr. Chapman:

We are unable to act favorably on your request to expand the present exemption for dimethyl sulfoxide to include use as a solvent or cosolvent within 1 day of harvest. The question of potentiation between DMSO and other chemicals precludes further exemption. We believe that tolerance proposals for DMSO would be necessary to support each combination; ie. DMSO + parathion in wheat. Sufficient information would be required to support the proposals for DMSO and to show that established tolerances for the individual pesticide would not be exceeded.

Sincerely,

Richard F. Mountfort *RFM*
Product Manager (23) *12/10/76*
Fungicide-Herbicide Branch
Registration Division (WH-567)



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF TOXIC SUBSTANCES

Honorable Mike McCormack
House of Representatives
Washington, D. C. 20515

Dear Mr. McCormack:

Thank you for your letter of August 8, 1978, on behalf of Mr. J. A. Chapman, General Manager of the Chemical Products Division of Crown Zellerbach. Crown Zellerbach has had a pesticide petition (4F1486) pending before the Agency which requests an exemption from the requirement of a tolerance or legal residue level for dimethyl sulfoxide (DMSO). Recently Mr. Chapman noted that the Agency has exempted a number of pesticidally inert ingredients from the tolerance requirement without similarly granting a tolerance exemption for DMSO. He feels the Agency is not reviewing the Crown Zellerbach petition by the same standards we have used for these other inert ingredients.

Let me first explain that EPA regulates pesticide products directly under the provisions of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). It also establishes tolerances or exemptions from tolerances for residues of chemicals remaining on crops treated with pesticide products under the authority of the Federal Food, Drug, and Cosmetic Act (FFDCA). A tolerance or tolerance exemption must be established for any pesticide and any inert ingredient of a pesticide formulation intended for use on a food or feed crop. Crops bearing residues of pesticides or inert ingredients lacking established tolerances or exemptions are considered adulterated and may be subject to seizure by the Food and Drug Administration.

The Crown Zellerbach petition requesting an exemption for DMSO has presented us some particular problems not shared by the exempted inerts listed in the July 11, 1978, Federal Register notice enclosed by Mr. Chapman. Specifically, DMSO has unique solvent characteristics, allowing it to penetrate cell tissues and thus possibly enhancing penetration of the pesticide dissolved in it. Enhanced penetration of the pesticide could result in residues exceeding tolerances established for the pesticide itself and thus present a possible health hazard from consumption of crops bearing the increased residues. These issues must be resolved before a tolerance exemption could be granted.

-2-

Given the nature of DMSO, we have told Crown Zellerbach that it would be necessary for them to submit petitions with supporting data for the establishment of finite tolerances for each combination of DMSO and particular pesticide on a given crop in order to assure that enhanced penetration of pesticide residues will not present undue risks. Crown Zellerbach feels that it would be more reasonable to deal with this problem by exempting DMSO itself from the tolerance requirement and by requiring those pesticide producers who wish to register pesticide products formulated with DMSO under the provisions of the FIFRA to submit data on the enhanced penetration of residues of their particular product.

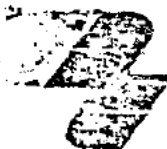
Because of the unique problems associated with exempting DMSO from the tolerance requirement, I have referred the petition to our Hazard Evaluation Division for a full review and reconsideration and have asked them to make a recommendation to me within a month. After I have received the recommendation, I will be in touch with you again to discuss our conclusions about the most appropriate way to satisfy the tolerance requirements of the FFDCA in the case of DMSO.

I appreciate Mr. Chapman's concern that the Agency handle the Crown Zellerbach petition in a reasonable and timely manner and hope you will reassure him of our efforts to resolve this issue promptly. In the meantime, if I may be of further service, please let me know.

Sincerely yours,

Edwin L. Johnson
Deputy Assistant Administrator
for Pesticide Programs

TSPX:ALINDSAY:acl:X58020:8/23/78 AL-5351
cc: TS(2) AL Region 10w/inc. Dave Ritter TS-769
 Dick Mountfort TS-767
 Doug Camp TS-767 w/inc. for ACTION
 Mike Conlon TS-769 w/inc. for ACTION ✓



CrownZellerbach
Chemical Products Division

1978

July 31, 1978

CERTIFIED MAIL -
RETURN RECEIPT REQUESTED

Federal Register Section
Technical Services Division (WH 569)
Office of Pesticide Programs
Environmental Protection Agency
Room 401 East Tower
401 M Street SW
Washington, D.C. 20460

Gentlemen:

Reference: Federal Register Vol. 43, No. 133 (6560-01)

The above reference proposes certain additional inert ingredients (or occasionally active ingredients) in pesticide formulations be exempted from tolerance requirements. The proposal lists various inert ingredients and concludes that the substances if used with good agricultural practices are useful and do not pose a hazard to the environment.

Approval of many of the proposed substances were based on the fact that they were previously cleared as food additives or were naturally occurring substances. These bases are inconsistent with the correspondence between your Agency and Crown Zellerbach relative to Crown Zellerbach's request to remove certain limitations on use of dimethyl sulfoxide (DMSO) as a pesticide solvent (Pesticide Petition 4F1486). Since March, 1974, Crown Zellerbach has supplied data on residue studies, feeding studies and toxicology information in support of this petition. The conclusions by your Agency for not approving removal of the limitations were based on a concern that DMSO may potentiate pesticides and that it would be necessary to propose tolerances for specific combination of DMSO with pesticides on specific crops. See attached.

It is surprising that your Agency would propose amending 40 CFR Part 180, thereby expanding the limits of the substances listed in the referenced Federal Register in that no potentiation data on specific pesticide combinations on specific crops were apparently submitted. If no data were submitted, then it would appear that since the substances are naturally occurring or were approved for one use they would not potentiate other active ingredients under another method of use.

Environmental Protection Agency

-2-

July 31, 1978

DMSO and its metabolites are naturally occurring in the environment (as evidenced by many studies, including one by your Agency) and DMSO is certainly less toxic and more volatile than most of the proposed substances.

We would appreciate your comments explaining the apparent inconsistency in the review process and data requirements.

Very truly yours,

J. A. CHAPMAN/hw


General Manager
Chemical Products Division

Attachment

cc: Mr. Sol Moser - w/a
Crown Zellerbach
Washington, D.C.

Sen. Henry M. Jackson - w/a
Sen. Warren G. Magnuson - w/a
Rep. Mike McCormack - w/a
Mr. Richard F. Mountfort, EPA

- PROPOSED RULES

29809

[6560-01]

[40 CFR Part 180]

IOPP-300014; FRL 924-71

TOLERANCES AND EXEMPTIONS FROM TOLERANCES FOR PESTICIDE CHEMICALS IN OR ON RAW AGRICULTURAL COMMODITIES

Proposed Exemption from Requirement of a Tolerance for Certain Inert Ingredients in Pesticide Formulations

AGENCY: Office of Pesticide Programs, Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: This notice proposes that certain additional inert ingredients (or occasionally active) ingredients in pesticide formulations be exempted from tolerance requirements. The proposal was submitted by various firms. This amendment to the regulations would permit the use of the exempted ingredients in pesticide formulations.

DATE: Comments must be received on or before August 10, 1978. Requests to refer this proposal to an Advisory

Committee must be received on or before August 10, 1978.

ADDRESS COMMENTS TO: Federal Register Section, Technical Services Division (WH-569), Office of Pesticide Programs, EPA, Room 401, East Tower, 401 M Street SW., Washington, D.C. 20460.

FOR FURTHER INFORMATION CONTACT:

Mr. David Ritter, Toxicology Branch, Registration Division (WH-567), Office of Pesticide Programs, DPA, 202-426-2680.

SUPPLEMENTARY INFORMATION: At the request of several interested persons, the Administrator is proposing to amend 40 CFR 180.1001 by exempting certain additional pesticide chemicals which are inert (or occasionally active) ingredients in pesticide formulations from tolerance requirements.

Inert ingredients are all ingredients which are not active ingredients as defined in 40 CFR 162.3(c), and includes,

but is not limited to the following types of ingredients (except when they have pesticidal efficacy of their own):

Solvents such as water; baits such as sugar, starches, and meat scraps; dust carriers such as talc and clay; fillers; wetting and spreading agents; propellants in aerosol dispensers; and emulsifiers. The term inert is not intended to imply nontoxicity; the ingredient may or may not be chemically active.

The preambles to proposed rulemaking documents of this nature include the common or chemical name of the substance under consideration, the name and address of the firm making the request for the exemption, and the toxicological and other scientific bases used in arriving at a conclusion of safety in support of the exemption.

The amendment to 40 CFR Part 180 which is adding § 180.1040 pertains to ethylene glycol, a specific inert ingredient which is associated with a restricted use pattern. The basis for that restriction is that there would be no reasonable expectation of residues in the raw agricultural commodity. This

Inert ingredient	Firm	Bases for approval
n-Alkyl(C ₈ -C ₂₄) amine acetate	Armak Co., 8401 West 47th St., McCook, Ill. 60525.	Previously cleared under 21 CFR 172.710. 90-day dog and rat feeding studies.
N,N-Bis(2-hydroxyethyl) alkylamines	do	Parent group previously cleared under 40 CFR 180.1001(d). 90-day dog and rat feeding studies.
N,N-Bis(2-omega-hydroxypolyoxyethylene) ethyl alkylamine	do	Parent compound previously cleared under 40 CFR 180.1001(d). No additional toxicologically significant exposure is expected from the proposed use.
Copper naphthenate	American Cyanamid Co., Princeton, N.J. 08540.	No reasonable expectation of residues on the raw agricultural commodities under applicable use restrictions.
Copper salts of neodecanoic acid and 2-ethyl hexanoic acid	do	Copper salts previously cleared under 21 CFR as food additives and 40 CFR 180.1001(b)(1). Copper is an essential nutrient. Tolerance of 1 ppm previously established for neodecanoic acid on cottonseed based on dog and rat studies ethyl hexanoic acid previously cleared under 21 CFR 172.515 as a synthetic flavoring and under 40 CFR 180.1001(d) as its alcohol form.
Corn syrup	Clinton Corn Processing Co., Clinton, Iowa 52732.	Human dietary constituent.
D and C green No. 8	Burroughs Wellcome Co., Research Triangle Park, Durham, N.C. 27709.	Previously cleared under 40 CFR 180.1001(d). No reasonable expectation of residues in eggs, meat, or milk.
D and C red No. 17	do	Do.
D and C violet No. 2	do	Do.
Dialkyl(C ₈ -C ₂₄) dimethyl ammonium chloride, the dialkyl(C ₈ -C ₂₄) derived from tallow.	Armak Co., 8401 West 47th St., McCook, Ill. 60525.	Previously cleared under 21 CFR 172.1010 in sanitizing solutions contacting food and 172.712 in sugar solids. Tallow fatty acids are natural body constituents.
Douglas-fir bark, ground	Weyerhaeuser Co., 505 North Pearl St., Centralia, Wash. 98521.	Indigestible and harmless naturally occurring substance.
FD and C blue No. 1	Burroughs Wellcome Co., Research Triangle Park, Durham, N.C. 27709.	Previously cleared under 40 CFR 180.1001(e). No reasonable expectation of residues in eggs, meat, or milk.
Glycerol mono-, di-, and triacetate	Armak Co., 8401 West 47th St., McCook, Ill. 60525.	Naturally occurring body substances.
o-Pinene	Hercules, Inc., Wilmington, Del. 19899.	GRAS under 21 CFR 172.515 as synthetic flavoring.
Polyoxyethylene (5) sorbitan monooleate	ICI United States, Inc., Wilmington, Del. 19887.	Previously cleared under 21 CFR as a direct human food additive
n-Propanol	do	Previously cleared under 21 CFR 172.515 as a synthetic flavoring.
Styrene-maleic anhydride copolymer	Arco Chemical Co., 1500 Market St., Philadelphia, Pa. 19101.	Styrene component previously cleared under 21 CFR 172.515 as a synthetic flavoring agent. Long-term toxicity studies for maleic anhydride component which is cleared under 40 CFR 180.1001(d).
Tartrazine	Burroughs Wellcome Co., Research Triangle Park, Durham, N.C. 27709.	Previously cleared under 40 CFR 180.1001(d). No reasonable expectation of residues in eggs, meat, or milk.

29810

PROPOSED RULES

inert cannot be used in any other manner except as specified in the regulation and as determined in a specific product registered by the Agency in accordance with the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended (86 Stat. 973, 89 Stat. 751, 7 U.S.C. 136(a) et seq.).

Based on the above information, available data on the chemistry of these substances, and a review of their use, it has been found that, when used in accordance with good agricultural practice, these substances are useful and do not pose a hazard to the environment. It is concluded, therefore, that the proposed amendments to 40 CFR Part 180 will protect the public health, and it is proposed that the amendments be established as set forth below.

Any person who has registered, or submitted an application for the registration of a pesticide under FIFRA which contains any of the ingredients listed herein, may request, on or before August 10, 1978, that this proposal be referred to an advisory committee in accordance with section 408(e) of the Federal Food, Drug, and Cosmetic Act.

Interested persons are invited to submit written comments on the proposed regulation. The comments must bear a notation indicating both the subject matter and the OPP document control number "OPP-300014". All written comments filed in response to this notice will be available for public inspection in the office of the Federal Register section from 8:30 a.m. to 4 p.m. Monday through Friday.

Dated: May 19, 1978.

DOUGLAS D. CAMPT,
Acting Director,
Registration Division.

AUTHORITY: Sec. 408(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 346a(e)).

It is proposed that Part 180, Subpart D, be amended by (1) deleting the items "N,N-Bis(2-(omega-hydroxypoly(oxyethylene)) ethyl) alkyl amines; * * *", "N,N-Bis(2-omega-hydroxypoly(oxyethylene)) ethyl alkyl amines; * * *", and "N,N-Bis(2-hydroxyethyl) alkylamine, where the alkyl groups (C₁₂-C₁₈) * * *" from the table in section 180.1001(d); (2) alphabetically inserting new items in the tables in section 180.1001 (c), (d), and (e); and (3) adding the new section 180.1040, as follows:

§ 180.1001 Exemptions from the requirement of a tolerance.

(c) * * *

Inert ingredients	Limits	Uses
Glycerol mono-, di-, and triacetate		Solvent, cosolvent.
n-Propanol		Solvent, cosolvent.

(d) * * *

Inert ingredients	Limits	Uses
n-Alkyl(C ₁₂ -C ₁₈)amine acetate		Surfactants, related adjuvants of surfactants.
N,N-Bis(2-hydroxyethyl) alkylamine, where the alkyl groups (C ₁₂ -C ₁₈) are derived from coconut, cottonseed, soya, or tallow acids.		Surfactants, related adjuvants of surfactants.
N,N-Bis 2-(omega-hydroxypoly(oxyethylene)) ethyl alkylamine; the reaction product of 1 mole N,N-Bis(2-hydroxyethyl) alkylamine and 3-60 moles of poly(oxyethylene) alkylamine, where the alkyl group (C ₁₂ -C ₁₈) is derived from coconut, cottonseed, soya, or tallow acids.		Do.
Copper naphthenate	Not more than 2.5 pct of formulation; application limited to before edible portions of plants begin to form.	Mercaptan scavenger in technical pesticide.
Copper salts of neodecanoic acid and 2-ethyl hexanoic acid	Not more than 1 pct of formulation; application limited to before edible portions of plants begin to form.	Do.
Diakyl(C ₁₂ -C ₁₈) dimethyl ammonium chloride, (C ₁₂ -C ₁₈) group from tallow		Surfactants, related adjuvants of surfactants.
Douglas-fir bark, ground		Solid diluent, carrier.

PROPOSED RULES

29811

(d) * * *

Inert ingredients	Limits	Uses
α-Pinene	Not more than 2 pct of formulation by weight.	Stabilizer.
Polyoxyethylene (5) sorbitan monooleate		Surfactants, related adjuvants of surfactants.
Styrene-maleic anhydride copolymer	For preemergence use only	Suspending or dispersing agent.

(e) * * *

Inert ingredients	Limits	Uses
Corn syrup		Sticker, attractant.
D and C green No. 6		Dye, coloring agent.
D and C red No. 17		Do.
D and C violet No. 2		Do.
FD and C blue No. 1		Dye, coloring agent.
α-Pinene	Not more than 2 pct of formulation by weight.	Stabilizer.
Tartrazine		Dye, coloring agent.

2. Part 180, Subpart D, is amended by adding the new § 180.1040 to read as follows:

§ 180.1040 Ethylene glycol; exemption from the requirement of a tolerance.

Ethylene glycol as a component of pesticide formulations is exempt from the requirement of a tolerance when used in foliar applications to peanut plants.

[FR Doc. 78-16812 Filed 7-10-78; 8:45 am]

[4310-84]

DEPARTMENT OF THE INTERIOR

Bureau of Land Management

[43 CFR Parts 3200, 3220]

GEOTHERMAL RESOURCES LEASING; GENERAL COMPETITIVE LEASES

Miscellaneous Amendments

AGENCY: Bureau of Land Management, Interior.

ACTION: Notice of comment period extension.

SUMMARY: Proposed rulemaking regarding the competitive leasing of geothermal resources was published on pages 20826 and 20827 of the FEDERAL REGISTER of May 15, 1978. Public comments were invited through July 14, 1978. This notice extends that comment period to August 15, 1978, to provide for more complete analysis of the rulemaking by interested persons and agencies.

DATE: Comment by August 15, 1978.

ADDRESS: Send comments to: Director (210), Bureau of Land Management, 1800 C Street NW., Washington, D.C. 20240. Comments will be available for public review at the above address from 7:45 a.m. to 4:15 p.m. on regular work days.

FOR FURTHER INFORMATION CONTACT:

Billy R. Templeton at the above address or telephone 202-343-8735.

ARNOLD E. PETTY,

Acting Associate Director.

JULY 6, 1978.

[FR Doc. 78-19048 Filed 7-10-78; 8:45 am]

[4910-60]

DEPARTMENT OF TRANSPORTATION

Materials Transportation Bureau

[49 CFR Part 191]

[Docket No. OPS-48; Notice 2]

TRANSPORTATION OF NATURAL AND OTHER GAS BY PIPELINE

Leak Reporting Requirements; Extension of Comments Period

AGENCY: Materials Transportation Bureau (MTB).

ACTION: Extension of comment period.

SUMMARY: This notice extends the period for comment to the notice published June 5, 1978 (43 FR 24478), from July 10, 1978, until August 10, 1978.

DATE: Comments must be received on or before August 10, 1978.

ADDRESS: Comments should identify the docket and notice number and be



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

Pesticide Petition 4F1486

15 FEB 1978

Mr. J. A. Chapman
Crown Zellerbach
Chemical Products Division
Camas, Washington 98607

Dear Mr. Chapman:

We are reluctant to pre-judge test results before a program is completed. The proposed protocol drawn up by Rhoads Scientific Company, however, will not suffice to permit expansion of the present exemption for dimethyl sulfoxide. As we have stated, it will be necessary to propose tolerances for specific combinations of the solvent with pesticides on specific crops. We do not believe that sampling, no matter how representative, of pesticides and crops, will be adequate for us to conclude that dimethyl sulfoxide should be further exempted. We are concerned both with applicator safety and effect on residue levels in the crop when DMSO is combined with toxicants.

Sincerely,

Richard F. Mountfort

Richard F. Mountfort
Product Manager (23)
Fungicide-Herbicide Branch
Registration Division (WH-567)

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FEB 21 1978
CH. P.D.



CrownZellerbach

Chemical Products Division

February 7, 1978

CERTIFIED MAIL -
RETURN RECEIPT REQUESTED

Fungicide-Herbicide Branch
 Registration Division (WH-567)
 United States Environmental Protection Agency
 Washington, D.C. 20460

Attn: Mr. Richard F. Mountfort
 Product Manager (23)

Gentlemen:

Subject: Pesticide Petition No. 4F1486

In your letter of October 21, 1977, and previous correspondence, you indicated the agency needs additional information to assess potential hazards involved when using dimethyl sulfoxide as a pesticide solvent. Specifically, the question is: would the use of this solvent potentiate the active ingredient such that established tolerances for the individual pesticide would be exceeded?

*meaning of
 potentiation here?
 (not too potent)*

Obviously, it would be impossible to develop information concerning every possible combination of pesticides, solvents and crops. However, we have contracted with a consulting firm, specializing in agrichemical research, to develop a protocol for a study that would provide meaningful information for our petition.

If you will note from the attached, the consultant proposes a comparative study of determining residues of pesticides selected from five structural classes on crops selected from five commodity groups. A residue comparison would be made between formulations involving the solvent, tetrahydrofurfuryl alcohol, and the solvent dimethyl sulfoxide. Tetrahydrofurfuryl alcohol was chosen because it is exempt from tolerance when applied to growing crops or raw agricultural commodities after harvest and it has properties similar to those of dimethyl sulfoxide (polar, water soluble, low volatility).

We would appreciate your study of the protocol. Before proceeding, we would like an indication from your agency whether results of this study, in addition to that we have provided over the past seven years, would provide sufficient information to answer the question of the potential hazard of dimethyl sulfoxide use on food crops.

Very truly yours,



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

Pesticide Petition 4F1486

21 OCT 1977

Mr. J. A. Chapman
Crown Zellerbach Corp.
Camas, Washington
98607

Dear Mr. Chapman:

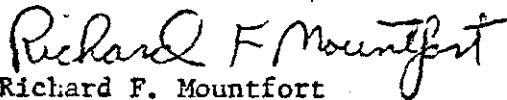
We have your letter of July 8, 1977 and do not agree that the proposed expansion of the present exemption for the solvent dimethyl sulfoxide should be granted. We are prepared to consider proposed tolerances for specific combinations of the solvent with pesticides on specific crops. An adequate evaluation of the potential hazards from use of dimethyl sulfoxide must include such proposals and sufficient data on each combination to describe the actual hazard and support the tolerance level for DMSO and the pesticide(s) involved. This action supports our responsibility under Section 3 of the Act, as amended, to register a pesticide if "it will perform its intended function without unreasonable adverse effects on the environment" and "when used in accordance with widespread and commonly recognized practice it will not generally cause unreasonable adverse effects on the environment" [Sections 3(c)(5)(C) and (D) of the Act]. Applicants for individual formulations will be required to provide sufficient information to support their proposed registrations. This does not, however, relieve you as proponent of this exemption request, from documenting your proposal sufficiently for us to assess the potential hazards involved. This you have not done and we feel you cannot do unless you propose and provide adequate support for finite tolerances(s). Our review of inert ingredients in pesticide formulations is being strengthened. Questions and decisions presently applied to DMSO may be required of other inerts. It is not sufficient, however, to quote prior exemptions for other solvents as a substitute for hazard assessment for dimethyl sulfoxide.

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CH. P.D.

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Your comments on the applicability of provisions of the Act to changes in a pesticide formulation are noted. Unauthorized changes in a registered pesticide formulation constitute a violation [Section 12(a)(1)(C) of the Act].

Sincerely,



Richard F. Mountfort
Product Manager (23)
Fungicide-Herbicide Branch
Registration Division (WH-567)



CrownZellerbach
Chemical Products Division

July 8, 1977

Fungicide-Herbicide Branch
Registration Division (WH-567)
United States Environmental Protection Agency
Washington, D. C. 20460

Attn: Mr. Richard F. Mountfort
Product Manager (23)

Gentlemen:

Subject: Pesticide Petition No. 4F1486
Your letters of December 10, 1976 and April 8, 1977

We assume from your letters your reluctance to act favorably on the subject petition stems from the following premises:

1. Producers of pesticide formulations may change the inert ingredients of the formulation without notifying the EPA, and if so, could produce a mixture containing solvents or adjuvants that would increase penetration and/or residues of the contained active ingredient.
2. DMSO has the ability of penetrating cell tissues and can enhance penetration of dissolved materials, while other solvents or adjuvants having tolerance exemption under 40 CFR 180.1001 do not.

If the first premise is correct, then we believe such action would be in conflict with FIFRA Pub. Law 92-516, Section 3. If a manufacturer of a final formulation changes the composition of the formulation and does not show evidence that satisfactory pesticide residues would result or that a hazard to humans and animals would not exist when the formulation is applied according to the label, it is our interpretation that violation of the public law would exist. Under FIFRA, manufacturers cannot change systems, incorporating even other exempted solvents, without your agency's approval. Such approvals would occur only after EPA's analysis of both the toxicological data of the new formulation (not only the active ingredient per se) and the concentration of the pesticide contained in the crop tissue. This interpretation of the existing laws has been reaffirmed through discussions with pesticide manufacturers.

The second premise, if it exists with your agency, is a common misunderstanding of the properties of DMSO. The fact that your conclusions were not supported by any scientific data points again to a judgment based on

Mr. Richard F. Mountfort

-2-

July 8, 1977

hearsay and rumors. DMSO does penetrate cell tissue, however, leading toxicologists have shown that most liquids, including water, penetrate tissue. The fact that all organic solvents exhibit acute dermal toxicity indicates permeation and absorption. The interesting aspect of DMSO is that it has a very low dermal toxicity (the lowest reported value of any existing organic solvent). Because of this low toxicity, the medical community in the early 1960's became interested in the possibility of using topical solutions of DMSO to carry drugs across skin membranes. There was considerable activity with this for a time, however, continual reported failures of enhanced penetration of the active ingredients brought this research to a halt throughout the country. It was found in most instances that the DMSO penetrated the skin but the drug product was left behind in the epidermis. In instances where some penetration was noted, the increase over other adjuvants was not significant. No commercial use of DMSO as a transport agent for a pharmaceutical exists.

The same activity occurred in the pesticide field. Knowing DMSO has low phytotoxicity, many leading companies conducted studies to determine the effectiveness of DMSO as a pesticide carrier, particularly in foliar applications. Not one found sufficient evidence of enhanced effects to warrant continued studies.

As to the concern that DMSO has greater ability to carry materials through living membranes than solvents and adjuvants currently having tolerance exemptions without limitations, much published literature contradicts such a claim. Ethanol and water are reported to be as effective in increasing skin permeability of phenol as DMSO (1). Xylene is reported to accelerate the skin penetration of drugs (2). Skin absorption of the steroid, estriol was found to be greater in corn oil than DMSO (3). Malathion, lindane and unbelliferone phosphonate dissolved in DMSO were less toxic to insects than when dissolved in acetone (4). Penetration of dodecyl sulfate 35^S through whole human abdominal skin was greater in a water solution than from a DMSO solution (5). In vitro absorption of the strongly polar insecticides, trichlorfon and dimethoate, through cattle skin was found to increase as polarity of the solvent (various alcohols) decreased and absorption of weakly polar insecticide butonate, exhibited the reverse result. Absorption of all three insecticides was greatly increased by addition of surfactants but addition of DMSO increased only the butonate resorption (6).

Control of spider mite by injection of dimethoate in cherry trees was found to be similarly effective when the pesticide was dissolved in ethanol, tetrahydrofuran, DMSO or as a water emulsion (7). Control of blossom blight on Bartlett pear was less with a streptomycin-water-DMSO foliar spray than with a straight streptomycin-water spray (8). Addition of X-77, DMSO, endothal and amitrole-T to paraquat solutions showed similar results in necrosis rate of hibiscus leaves (9).

Mr. Richard F. Mountfort

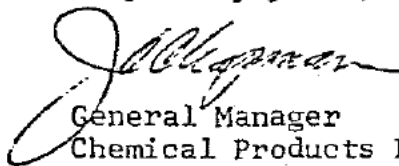
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July 8, 1977

We feel there is sufficient evidence to show that DMSO cannot be cited as being more of a potentiator than any of the tolerance exempt solvents and adjuvants under 40 CFR, 180.1001 (c) and (d). Further, that if DMSO is used in a formulation developed by a pesticide manufacturer, full toxicological and residue data must be provided to your agency as required under FIFRA and determination as to the formulation's safety can be made at that time.

Therefore, considering these aforementioned safeguards, in addition to the previously submitted data, we request approval of Petition No. 4F1486.

Very truly yours,



J. A. CHAPMAN/hw

General Manager
Chemical Products Division

cc: Mr. John Ritch
Dr. Martin Rogoff

- (1) Roberts, et al, Univ. Sydney, J. Pharm. Pharmacol, 1975, 27(8) 599-605 (England)
- (2) Creasey, et al, Brit. J. Dermatol, 1971, 85(4), 368-80 (England)
- (3) Jones, et al, Poultry Science, 1967, 46(1), 249-250.
- (4) Enriquez, et al, Bol. Real Soc. Espan. Hist. Natur., Secc. Biol., 1969, 67(1-2), 71-4, C.A. 73, 86878j.
- (5) Embery et al, Brit. J. Dermatol. Suppl. 1969, 81(4), 63-8 (England)
- (6) Dedek, et al, Arch. Exp. Veterinaarmed. 1975, 29(6), 857-68 (Germany)
- (7) Harries, F.H., J. of Economic Entomology, 1965, 58(4), 631-634.
- (8) Zehr, E. I., Phytopathology, 1968, 58, 1624-1629.
- (9) Bovey, R. W., Miller, F.R., Weed Res., 1968, 8, 128-135



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

8 APR 1977

Crown Zellerbach
Attention: J. A. Chapman
Chemical Products Division
Camas, Washington 98607

Gentlemen:

Subject: PESTICIDE PETITION NO. 4F1486
Your letters of January 3 and March 18, 1977

We do not believe that you have submitted sufficient information to permit further exemption for the solvent DMSO or to allay concern over potentiation. The solvent and a broad range of toxicants could be combined as a result of further exemption. You have mentioned oral toxicity studies with five pesticides but have presented no information on other routes of exposure. DMSO readily penetrates cell tissue, animal and plant, and can enhance penetration by other compounds. Your tolerance proposals should not only show that hazard is not increased in combination, but that established tolerances are not affected.

Sincerely,

Richard F Mountfort
Richard F. Mountfort
Product Manager (23)
Fungicide-Herbicide Branch
Registration Division (WH-567)

J.A.C.

RECEIVED
APR 14 1977
CH. P.D.

End
of
Document

Pesticide Petition 4F1486

15-11-1978

Mr. J. A. Chapman
Crown Zellerbach
Chemical Products Division
Camas, Washington 98607

Dear Mr. Chapman:

We are reluctant to pre-judge test results before a program is completed. The proposed protocol drawn up by Rhoads Scientific Company, however, will not suffice to permit expansion of the present exemption for dimethyl sulfoxide. As we have stated, it will be necessary to propose tolerances for specific combinations of the solvent with pesticides on specific crops. We do not believe that sampling, no matter how representative, of pesticides and crops, will be adequate for us to conclude that dimethyl sulfoxide should be further exempted. We are concerned both with applicator safety and effect on residue levels in the crop when DMSO is combined with toxicants.

Sincerely,

Richard F. Mountfort *RFm*
Product Manager (23)
Fungicide-Herbicide Branch
Registration Division (WH-567)

WH-567:FHB:RFMountfort:mmq:rm351 WSME,x51397:2-15-78

*Bob - did we see this proposal or are these comments Mountfort's?
This should be filed in PP 4F1486*

*JHC
2/24/78*

No. Rll 2/26/78.

End
of
Document



CrownZellerbach

Chemical Products Division

February 7, 1978

CERTIFIED MAIL -
RETURN RECEIPT REQUESTED

Fungicide-Herbicide Branch
 Registration Division (WH-567)
 United States Environmental Protection Agency
 Washington, D.C. 20460

Attn: Mr. Richard F. Mountfort
 Product Manager (23)

Gentlemen:

Subject: Pesticide Petition No. 4F1486

In your letter of October 21, 1977 and previous correspondence, you indicated the agency needs additional information to assess potential hazards involved when using dimethyl sulfoxide as a pesticide solvent. Specifically, the question is: would the use of this solvent potentiate the active ingredient such that established tolerances for the individual pesticide would be exceeded?

Obviously, it would be impossible to develop information concerning every possible combination of pesticides, solvents and crops. However, we have contracted with a consulting firm, specializing in agrichemical research, to develop a protocol for a study that would provide meaningful information for our petition.

If you will note from the attached, the consultant proposes a comparative study of determining residues of pesticides selected from five structural classes on crops selected from five commodity groups. A residue comparison would be made between formulations involving the solvent, tetrahydrofurfuryl alcohol, and the solvent dimethyl sulfoxide. Tetrahydrofurfuryl alcohol was chosen because it is exempt from tolerance when applied to growing crops or raw agricultural commodities after harvest and it has properties similar to those of dimethyl sulfoxide (polar, water soluble, low volatility).

We would appreciate your study of the protocol. Before proceeding, we would like an indication from your agency whether results of this study, in addition to that we have provided over the past seven years, would provide sufficient information to answer the question of the potential hazard of dimethyl sulfoxide use on food crops.

Very truly yours,

General Manager
 Chemical Products Division

J. A. CHAPMAN/hw
 Attachment

Rhoads Scientific Company
4620 Edison Avenue, Suite B
Colorado Springs, CO 80915

Project Number 1002
January 31, 1978

PROPOSAL TO: Crown Zellerbach
Chemical Products Division
Camas, Washington 98607

TITLE: Comparative Pesticide and Herbicide Residue Study:
Determination of the Effect of Employing Dimethylsulfoxide As A Solvent on the Residue Levels of Compounds Representing Five Classes of Pesticides or Herbicides in Common Use Following Their Individual Application to Five Commercially Significant Types of Crops.

INTRODUCTION:

Staff members of Rhoads Scientific Company have reviewed the information supplied by Mr. James A. Chapman of Crown Zellerbach, Chemical Products Division, concerning the questions raised by the U.S. Environmental Protection Agency (EPA) relative to the use of dimethylsulfoxide (DMSO) as a solvent in agricultural pesticide and herbicide formulations. In view of the extensively documented capability of DMSO to facilitate cell wall penetration, EPA has expressed concern that employment of this solvent in agricultural pesticide and herbicide formulations could result in increased crop residues of the parent compound and/or metabolites which might exceed accepted tolerance levels. Obviously, it is neither technically nor financially feasible to test DMSO as a formulation ingredient for all registered agricultural pesticide and herbicide applications to food and/or forage crops. Consequently, the staff of Rhoads Scientific Company proposes to test five compounds, representing five structural classes of pesticides and herbicides in common use, to determine if any potentiation of residue levels is produced by the use of DMSO in the individual application of these compounds to five kinds of plants, representing five commercially significant types of food and/or forage crops grown in this country.

Although the proposed experiment, described in detail below, is simple and relatively limited in scope, it will provide an answer to the basic question about potentiation of residue levels. In the event that the application of the test compounds in aqueous DMSO results in higher residue levels, in one or more cases, than in a similar application in aqueous tetrahydrofurfuryl alcohol (THFA), Rhoads Scientific Company would agree that it would be necessary to determine the residue potentiation capacity of DMSO for specific applications of compounds of that structural class

Project Number 1002
January 31, 1978
Page 2

or classes of pesticide or herbicide. However, if no significant differences in residue levels are observed between applications in aqueous DMSO and aqueous THFA, it would be highly unlikely that the general use of DMSO in pesticide and herbicide formulations would result in an increase in pesticide or herbicide residues exceeding accepted tolerance levels.

One final point should be made regarding the proposed experiment. Mr. Chapman of Crown Zellerbach has indicated that the probable method of use of pesticide or herbicide formulations containing DMSO would involve extensive dilution with water either prior to or during the normal types of spray application. Therefore, Rhoads Scientific Company has proposed to employ a 1:20 (v/v) DMSO:H₂O solution on the basis that such a solution would represent a DMSO concentration of several magnitudes greater than the probable use pattern. Since the solution proposed for application to the individual plants will contain 2.0 mg of active ingredient and 110 mg of DMSO, this mixture would correspond to a concentrated formulation containing one part by weight of active ingredient per 54 parts by weight of solvent which is much higher than the 1:9 active ingredient: solvent ratio customarily found in formulations. As a control, Rhoads Scientific Company has proposed to employ a 1:20 (v/v) THFA:H₂O solution on the basis that THFA is also a polar solvent which is very soluble in water, and therefore, a good standard for comparison.

EXPERIMENTAL PROTOCOL:

Forty microcuries of each of the carbon-14 labeled test compounds, having a specific activity of 1.0 μ Ci/mg or greater, will be purchased from Pathfinder Laboratories, Inc., St. Louis, Missouri or obtained directly from the individual pesticide or herbicide manufacturers. In each case, the radiochemical purity of the test compounds will be established by thin layer chromatography followed by radioautography. The test compounds employed will be pesticides and herbicides, actually in current use, representing the following structural classes: carbamates, substituted ureas, dinitroanilines, organophosphates, and phenoxyacetic acids. For toxicity control purposes, unlabeled analytical standards of the test compounds will also be acquired; however, in this case, no purity data will be generated.

The test plants will be grown in the greenhouse facility of Ecology Consultants, Inc., Fort Collins, Colorado. Thirty healthy plants of each type, weighing approximately 100 grams each, will be grown in individual six inch pots. Twenty of the most vigorous plants will be selected for test purposes; whereas,

Project Number 1002

January 31, 1978

Page 3

the remaining ten will be retained for toxicity control purposes. The plants employed will be tomatoes, corn, radishes, alfalfa, and soybeans respectively representing a fruit crop, a cereal crop, a root crop, a forage crop, and a seed crop.

Five days prior to the application of the radiolabeled compounds, the toxicity control plants will be individually treated with the unlabeled test compounds at the same rate (circa 2.0 mg per plant) which will be used for the radiolabeled compounds. Each test compound will be applied to two control plants of each type. One plant will be treated with the test material dissolved in 2.1 ml of aqueous DMSO and the other with the material dissolved in 2.1 ml of aqueous THFA. The plants will be carefully observed during the first 24 hours following treatment and all indications of adverse reaction recorded. Since the proposed treatment rate corresponds to approximately 0.80 pounds per acre, which is comparable to normal application rates, some immediate toxic effects could be generated by the herbicides used. Naturally, if severe phytotoxicity is observed, that part of the test will be postponed until different species of the same type of crop and/or different compounds of the same structural class can be tested to establish a combination producing little or no observable toxicity.

The application of the radiolabeled test compounds will be conducted in a manner similar to that used during the toxicity control phase of the experiment; however, in this case, material balance data will be generated for each individual application. Twenty microcuries of each carbon-14 labeled pesticide or herbicide will be individually dissolved in 21.0 ml of 1:20 (v/v) DMSO:H₂O. In the event that the test material is not entirely soluble in such a solution, Tween 80 will be added, as necessary, to produce a homogeneous mixture. The resulting solution will be divided into ten 2.1 ml aliquots. Each aliquot will be placed in a 15 ml conical tube and the radiocarbon content of the individual tubes determined by assaying two 5 µl aliquots by liquid scintillation spectrometry. The contents of a single tube will then be applied, with the aid of two 0.1 ml rinses of aqueous DMSO, to an individual test plant by painting the solution on the leaves with a small brush. Following application, the tube and the brush will be retained for assay of the residual radiocarbon by thorough rinsing of the tube and the brush with 10 ml of ethanol and subsequent liquid scintillation counting of two 1 ml aliquots of that rinse.

Two plants of each type will be treated per radiolabeled test compound dissolved in aqueous DMSO and two per radiolabeled test compound dissolved in aqueous THFA. The application of the test materials in aqueous THFA will, of course, be identical to that

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described previously for aqueous DMSO. After completion of the total treatment procedure, the plants will be allowed to stand under normal greenhouse conditions for 24 hours before they are harvested. At harvest, each entire plant, including the major root or roots, will be collected. Surface residue will be stripped from each plant by dipping the foliage in three successive beakers containing sufficient benzene to cover all but the root system. In each case, the benzene washes will be retained for subsequent measurement of the volume and assay of an appropriate aliquot by liquid scintillation spectrometry to determine the total radiocarbon removed from the surface of the plant. Following the washing procedure, the plants will be placed in individual plastic sacks, frozen, and stored at -10°C prior to assay.

The individual plants will be assayed for total radiocarbon residue (TR) by combustion and subsequent assay of the carbon-14 dioxide produced by liquid scintillation spectrometry. For this purpose, each entire plant will be very finely ground and thoroughly mixed by homogenization in a Waring blender in the presence of dry ice. Two sub-samples, weighing approximately 0.2 gram, will be removed from each of the resulting frozen whole plant homogenates for combustion assay of the total carbon-14 labeled residue (TR).

Following the determination of the total residue (TR), the individual total extractable residues (TER) will be determined by extracting 10 grams of each of the whole plant homogenates three times with aqueous methanol followed by assay of the combined extracts from each homogenate by liquid scintillation spectrometry. For this purpose, 10 grams of the individual whole plant homogenates will be placed in a Waring blender and thoroughly homogenized with 50 ml of 2:1 (v/v) methanol:water by blending at high speed for 5 minutes. The resulting liquid homogenate will be subjected to vacuum filtration on Whatman #1 paper. The filtrate will be transferred to a 250 ml graduated cylinder. The insoluble material will then be returned to the blender and homogenized with a fresh 50 ml portion of aqueous methanol and the resulting liquid homogenate subjected to vacuum filtration as before. The filtrate obtained will be added to that isolated previously and the blending and extracting process repeated for the third time. Following this final extraction, the insoluble material, isolated by vacuum filtration, will be spread on aluminum foil and allowed to dry at ambient temperature. The final filtrate or extract will be added to those obtained previously. After thorough mixing, the volume of the combined extracts will be measured and two 1 ml aliquots withdrawn for assay by liquid scintillation spectrometry.

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Page 5

Following the determination of the total residue (TR), and the total extractable residue (TER), the total bound residue (TBR) will be determined by combustion of the insoluble fraction from the aqueous methanol extraction and subsequent liquid scintillation assay of the carbon-14 labeled carbon dioxide produced. For this purpose, the dried retentate from each whole plant extraction procedure will be weighed, and two samples weighing approximately 0.2 gram, will be removed for combustion assay of the total carbon-14 labeled bound residue (TBR).

INTERPRETATION OF EXPERIMENTAL RESULTS:

Obviously, this proposed experiment has been designed to provide complete radiocarbon material balance in all phases. Differential and/or accelerated losses by evaporation and/or expiration of radiolabeled carbon dioxide will be detected by failure to obtain a total material balance. Differential rates of absorption will be detected by differences in the total residue (TR) values. In the event that total absorption is observed or the amount of material absorbed is the same for both application vehicles, the TER:TBR ratios may provide some evidence of accelerated absorption and/or metabolism, should that have occurred. In summary, although this proposed experiment is simply designed, it will generate evidence of any potentiation of residue levels resulting from the use of DMSO.

CALCULATIONS AND NOTES ON THE METHODOLOGY:

All counting samples will be counted for 20 minutes or until 10,000 counts have accumulated. Counting efficiencies will be determined by the external standard ratio method or by the addition of an internal standard.

Since the 0.2 gram combustion samples are the smallest experimental samples to be assayed, it is of interest to calculate the limit of detectability for those samples. Since the normal background in the area in which Rhoads Scientific Company is located averages 50 dpm, the customary limit for counting detection is 50 dpm above background. For a 0.2 gram sample actually assayed, this corresponds to 250 dpm/gram. Since the radiolabeled test compounds will have a minimum specific activity of 1.0 $\mu\text{Ci}/\text{mg}$ or 2220 dpm/ μg , the limit of detectability will be:

$$\frac{250 \text{ dpm/g}}{2220 \text{ dpm}/\mu\text{g}} = 0.11 \text{ parts per million}$$

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On the basis of a 20 minute total counting time, an average background of 50 dpm and a limit of counting detection of 50 dpm above background, the total counting error at the limit of detectability can be calculated as follows:

$$\text{BACKGROUND ERROR} = \frac{\sqrt{50 \times 20}}{20} = 1.6 \text{ dpm}$$

$$\text{SAMPLE ERROR} = \frac{\sqrt{100 \times 20}}{20} = 2.2 \text{ dpm}$$

$$\text{TOTAL ERROR} = \sqrt{(1.6)^2 + (2.2)^2} = 3.5 \text{ dpm}$$

Thus, a sample counting at a limit of detectability would exhibit a total counting error of $3.5/50 \times 100 = 7.0$ percent.

An estimate of the application rate in pounds per acre can be made from the known application of 2.0 mg to each individual plant grown in a six inch pot. Since four pots would cover one square foot, this rate of application corresponds to 8.0 mg/ft². Since there are 43,560 ft²/acre, this is a rate of 348,480 mg/acre or 348.48 grams/acre. Applying the conversion factor of 0.0022 pounds/gram, this rate corresponds to approximately 0.80 pounds/acre.

An estimate of the application concentration in pounds per 100 gallons can be made from the known application of 2.0 mg in 2.1 ml of solvent. Since there are 378,540 ml per 100 gallons, this corresponds to 360,514 mg per 100 gallons or 360.5 g per 100 gallons. Applying the conversion factor of 0.0022 pounds/gram, this concentration corresponds to approximately 0.8 pounds per 100 gallons.

RHOADS SCIENTIFIC COMPANY

Margaret E. Ackerman
By
M.E. Ackerman, Ph.D.
Director of Metabolism and
Radiochemistry

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of
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pp 4F1486

21 OCT 1977

Pesticide Petition 4F1486

Mr. J. A. Chapman
Crown Zellerbach Corp.
Camas, Washington
98607

Dear Mr. Chapman:

We have your letter of July 8, 1977 and do not agree that the proposed expansion of the present exemption for the solvent dimethyl sulfoxide should be granted. We are prepared to consider proposed tolerances for specific combinations of the solvent with pesticides on specific crops. An adequate evaluation of the potential hazards from use of dimethyl sulfoxide must include such proposals and sufficient data on each combination to describe the actual hazard and support the tolerance level for DMSO and the pesticide(s) involved. This action supports our responsibility under Section 3 of the Act, as amended, to register a pesticide if "it will perform its intended function without unreasonable adverse effects on the environment" and "when used in accordance with widespread and commonly recognized practice it will not generally cause unreasonable adverse effects on the environment" [Sections 3(c)(5)(C) and (D) of the Act]. Applicants for individual formulations will be required to provide sufficient information to support their proposed registrations. This does not, however, relieve you as proponent of this exemption request, from documenting your proposal sufficiently for us to assess the potential hazards involved. This you have not done and we feel you cannot do unless you propose and provide adequate support for finite tolerances(s). Our review of inert ingredients in pesticide formulations is being strengthened. Questions and decisions presently applied to DMSO may be required of other inerts. It is not sufficient, however, to quote prior exemptions for other solvents as a substitute for hazard assessment for dimethyl sulfoxide.

2

Your comments on the applicability of provisions of the Act to changes in a pesticide formulation are noted. Unauthorized changes in a registered pesticide formulation constitute a violation [Section 12(a)(1)(C) of the Act].

Sincerely,

Richard F. Mountfort *RFm*
Product Manager (23)
~~Fungicide-Herbicide Branch~~
~~Registration Division (WH-567)~~

WH-567:FHB:RFMountfort:mmq:rm351 WSME,x51397:8/1/77

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Quack
Hammel
PP 4F1486

8 APR 1977

gke
7/11/77

Crown Zellerbach
Attention: J. A. Chapman
Chemical Products Division
Camas, Washington 98607

Gentlemen:

Subject: PESTICIDE PETITION NO. 4F1486
Your letters of January 3 and March 18, 1977

We do not believe that you have submitted sufficient information to permit further exemption for the solvent DMSO or to allay concern over potentiation. The solvent and a broad range of toxicants could be combined as a result of further exemption. You have mentioned oral toxicity studies with five pesticides but have presented no information on other routes of exposure. DMSO readily penetrates cell tissue, animal and plant, and can enhance penetration by other compounds. Your tolerance proposals should not only show that hazard is not increased in combination, but that established tolerances are not affected.

Sincerely,

Richard F. Mountfort
Product Manager (23)
Fungicide-Herbicide Branch
Registration Division (WH-567)

WH-567:FHB:RFMountfort:mmq:rm351 WSME,x51397:4/7/77

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1377

PP# 4F1486. Proposed exemption for DMSO. Comments on the results of the method trial and letters of 1/3/77 and 3/8/77.

R. J. Hummel, Chemist, Chemistry Branch
Registration Division (WH-507)

Product Manager 23 (R. Mountfort) and Toxicology Branch

THRU: Chief, Chemistry Branch

In our review of 4/9/76, we recommended that the proposed exemption for DMSO be granted and that Section 190.1001(d) be amended to read as follows:

<u>Inert ingredients</u>	<u>Limit</u>	<u>Uses</u>
Dimethyl sulfoxide	Not to be applied within 24 hours of harvest. Not to be applied to crops which may be used for grazing, forage, silage or fodder after emergence from soil.	Solvent, cosolvent

Subsequently, it was decided that it might be more appropriate to establish tolerances for residues of DMSO resulting from its use as a solvent or cosolvent. If it were deemed advisable to establish tolerances for DMSO residues, our memo of 7/20/76 suggested the following levels:

10 ppm in or on crops
0.2 ppm in eggs and the meat, fat and meat byproducts of cattle, goats, hogs, horses, poultry and sheep
0.05 ppm in milk

However, we noted that prior to establishing these tolerances, we would require suitable methodology for meat, milk, poultry and eggs and successful method trials on crops, milk and meat.

The petitioner's method was extensively modified in our laboratory (see Hakhijani memo of 1/5/77). The modified method was tried out on lettuce and soybeans at our laboratory and on milk and beef liver at the petitioner's laboratory. The following results were obtained.

-2-

<u>Substrate</u>	<u>Fortification levels (ppm)</u>	<u>Recoveries (%)</u>	<u>Blanks (ppm)</u>
lettuce	1,10	75-100	<0.3
soybeans	1,10	74-115	<0.3
milk	0.1,0.2	67-70	0.04,0.06
beef liver	0.2,0-4	101-117	0.09,0.1

From these, we conclude that the modified method is adequate to enforce tolerances of 10 ppm on crops and 0.2 ppm in eggs and meat. Since apparent residues in milk were 0.04-0.06 ppm, the method would not be adequate to enforce a tolerance of 0.05 ppm in milk. However, it would be adequate to enforce a tolerance of 0.1 ppm.

In the reject letter of 12/10/76 (R. F. Mountfort), the petitioner was informed that data for every pesticide/DMSO combination would be needed to show that established tolerances for the individual pesticide would not be exceeded. In response, the petitioner has stated that they can find no evidence of DMSO's potentiating pesticide residues in the literature and has asked for the scientific basis for our request.

In the D. L. Ritter review of 9/9/74, TOX deferred to us as to whether the use of DMSO in pesticide formulations may result in higher-than-legal residues of such pesticides and/or their metabolites in RAC's. In our review of 10/22/74 (R. Beyak), we replied that we had no data related to this question and agreed that the unique solvent characteristics of DMSO present a possibility that residue levels of the pesticide may be affected. Consequently, in the reject letter of 12/2/74 (L. Zink), the petitioner was requested to submit data demonstrating the effects of DMSO on the residue levels of pesticides and/or their metabolites.

In a conference on 1/23/75, TOX and CHM reviewers agreed with the petitioner that DMSO potentiation of residue levels is a question that registrants of new DMSO-containing formulations will have to answer at the time of registration. The decision to require data on DMSO potentiation of residue levels from the petitioner at this time rather than from registrants at the time of registration was made by the Pesticides Science Officer (PSO).

Conclusions and Recommendations

1. a. Adequate analytical methods are available to enforce tolerances for DMSO residues in or on crops at 10 ppm and in meat, fat and meat byproducts of cattle, goats, hogs, horses, poultry and sheep at 0.2 ppm.

b. The available analytical method is not adequate to enforce a tolerance of 0.05 ppm for DMSO residues in milk. However, it would be adequate to enforce a tolerance of 0.1 ppm.

-3-

2. a. Due to the limitations of the available analytical methodology, we suggest that any tolerance for DMSO residues in milk be established at a level of 0.1 ppm. TOX should be consulted as to whether the available toxicological data will support this higher tolerance level for milk.

b. Toxicological considerations permitting, we could recommend for the following tolerances for DMSO residues:

- 10 ppm in or on crops
- 0.2 ppm in the meat, fat and meat byproducts of cattle, goats, hogs, horses, poultry and sheep and in eggs
- 0.1 ppm in milk.

3. The unique solvent characteristics of DMSO present a possibility that residue levels of pesticides formulated in DMSO may be affected. In a conference on 1/23/75, TOX and CHM reviewers agreed with the petitioner that DMSO potentiation of residue levels is a question that registrants of new DMSO-containing formulations will have to answer at the time of registration. The decision to require data on DMSO potentiation of residue levels from the petitioner at this time rather than from registrants of DMSO-containing formulations at the time of registration was made by the PSO.

R. J. Hummel, Ph.D.

cc: TOX:EEE:FDA:CHM (3)

WH-567:RJHUMMEL:mer:Rm 108:MSME:X62610:4/1/77

RDI:RSQUICK:3/24/77:JGCUMMINGS:3/1231/77

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CrownZellerbach
Chemical Products Division



March 8, 1977

Fungicide-Herbicide Branch
Registration Division (WH-567)
United States Environmental Protection Agency
Washington, D.C. 20460.

Attn: Mr. Richard F. Mountfort
Product Manager (23)

Gentlemen:

Petition 4Fl486

As yet I have not received a response to my letter of January 3, 1977. It is regrettable that an industrial firm complies beyond the letter of the law over the course of several years during the petitioning process and is treated by your Agency in such a poor way. If you are unable to respond in a scientific manner, I will assume your position on Petition 4Fl486 is arbitrary and further action by us will necessarily assume prejudice on your part.

Very truly yours,

J. A. CHAPMAN/hw

General Manager
Chemical Products Division

cc: Mr. John Ritch
Dr. Martin Rogoff

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of
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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

PP#4F1486. Method try-out for DMSO in milk, beef
 SUBJECT: liver, lettuce, and soybeans

DATE: January 5, 1977

FROM: Gobind P. Makhijani, Chemist
 Chemistry Branch, RD

TO: Mr. Joseph G. Cummings, Branch Chief
 Chemistry Branch, RD

THRU: Mr. R. W. Storherr, Section Leader
 Chemistry Branch, RD *RWS.*

In response to the request of Dr. R. J. Hummel, chemist, CB, RD, of June 17, we have just finished satisfactorily a method trial on dimethyl sulfoxide, DMSO. The method used was our modification of the Crown Zellerbach Corporation analytical method for DMSO in their Pesticide Petition No 1E1017, amended April 23, 1971. The modification of the method was developed and tested on 2 crops in Chemistry Branch Laboratory, Building #048 before closure. The final analytical work was performed at the Company laboratory, Camas, Washington.

Duplicate samples of soybeans and lettuce fortified at zero, 1.0 ppm, and 10.0 ppm were carried through the modified method. The EPA modified DMSO method for extraction, cleanup, and determination on GLC-FPD (sulfur mode) is as follows:

1. Extract samples with methanol^a: - Blend 30g of crop or 90g of milk and liver with 125 ml MeOH (250 ml for 90g milk or liver) for 5-10 minutes with 10 g Celite 545. Filter through a bed of Celite 545.
 2. Concentrate an appropriate aliquot to the aqueous phase at 50°C: - For milk and liver concentrate 109 ml aliquot (30g) to 25-30 ml. For crops concentrate a 50 ml aliquot (10g) to 10-15 ml.
- ^aTheoretical vol= 150.5 ml if 30g crop contains average of 85% water; 125 ml plus 25.5 ml. In case of soybeans and (or other dry crop, add 22.5 ml H₂O to 30g of soybeans before MeOH extraction)
3. Quantitatively transfer the aqueous concentrate to a 125 ml separatory funnel. Extract sample with either 2 times with 50 ml or 2 x 100 ml petroleum ether* depending upon the size of aliquot (10 or 30g). Discard the petroleum ether extracts.
 4. Extract sample 3 times with 75 ml CHCl₃. Dry each extract by passing thru a short anhyd Na₂SO₄ column. Rinse column with 25 ml CHCl₃. Collect all eluates and rinses in a 500 ml Erlenmeyer flask.

*Hexane may be used

5. Concentrate on rotary vacuum evaporator (40°C) to approximately 1 ml. Transfer to a graduated centrifuge tube using a disposable pipet and CHCl_3 rinses. Concentrate sample in 40°C water-bath with a gentle jet of nitrogen to near-dryness and make to 1 ml vol with MeOH. Inject into GLC having a FPD with sulfur filter.

GLC Conditions:

1. Columns:
 - a. Glass column, 6' x 3 mm i.d., packed with 15% Carbowax 20 M on Chromosorb W-AW, DMCS, 80-100 mesh. Column temperature = 150°C. Gas flows - Nitrogen= 100 ml/min; Hydrogen= 200 ml/min; Air= 40 ml/min; Oxygen= 20 ml/min.
 - b. Teflon column, 6' x 1.5 mm i.d. packed with 20% FFAP on Gas Chrom Q, 60/80 mesh. Column temperature = 145°C. Condition overnight. Gas flows - Nitrogen= 95 ml/min; Hydrogen= 100 ml/min; Air= 100 ml/min; Oxygen= 20 ml/min.

The following results for lettuce and soybeans were obtained at Beltsville, Building #048, using the 15% Carbowax 20 M column:

A. Lettuce

Sample No.	ppm of DMSO added	PPM OF DMSO found	% Recovery (Blank value not deducted)
1	none	<0.3 ppm	---
2	none	<0.3 ppm	---
3	10.0	7.5	75
4	10.0	9.0	90
5	1.0	1.0	100
6	1.0	1.0	100

B. Soybeans

1	none	<0.3 ppm	---
2	none	<0.3 ppm	---
3	10.0	93	93
4	10.0	7.4	74
5	1.0	1.1	110%
6	1.0	1.15	115

No precautions were taken to avoid the exposure of sample to air. The peak for DMSO appeared at the stated retention time of 2.4 minutes; the peaks were sharp. The background for the control samples for both crops was excellent. We recorded very small interfering peaks at the retention time of DMSO in the controls of both the crops equivalent to less than 0.3 ppm.

Preliminary work was also carried out at the Beltsville laboratory for the analysis of milk samples at zero and 1.0 ppm level. The checks for the milk control samples recorded a very small peak at the retention time of DMSO equivalent to 0.1 ppm. In addition to this, we recorded a large and overscale peak at the retention time of 8 minutes. (Subsequent investigations at Crown Zellerbach Corp. Laboratory at Camas, Washington, showed that the latter peak was apparently due to presence of dimethyl sulfone). The milk samples fortified at 1.0 ppm level gave nearly 100% recoveries.

The trial was suspended because building 048 was closed for health and safety reasons. Further work was resumed at Crown Zellerbach Laboratory, Camas, Washington from Dec. 6th to Dec. 16th. The petitioner provided us with a Hewlett Packard GLC system equipped with FPD detector. A teflon 8 ft x 1.5 mm id column packed with 15% carbowax 20 M on chromosorb W AWD MCS - 80/100 mesh (from the same batch used for our work at Beltsville lab) was installed.

In spite of conditioning for 2 days, the background recorded on the chromatogram was poor - this may have been due to the bleeding of carbowax at 150°C. Since we were looking for very low fortification levels of DMSO from milk and liver, we had to change the column packing. We then installed a teflon 6 ft x 1 1/2 mm - id packed with 20% FFAP on Gas Chrom Q-60/80 mesh. After conditioning overnight at 175°C, we obtained excellent response for DMSO at the column temperature of 145°C and detector temperature of 158°C and nitrogen flow set at 95 ml/min. The retention time for DMSO was 2.36 min. We were able to record a measurable sharp peak for 1 ng of DMSO (0.7 mm) at the sensitivity setting of Range 100, Att 32. Since we were asked to fortify milk samples at 0.05 and 0.1 ppm levels of DMSO, we had to increase the sample size from 10g to 30g and a few other modifications were also made from our procedure for lettuce and soybeans. These changes are incorporated in the outlined method.

Duplicate reagent blanks were taken through the entire procedure and no precautions were taken to avoid exposure of samples to air. The final samples were made to 1.0 ml in methanol and 4.5 microliter aliquots (equivalent to 90 mgm of the sample) were injected in the GLC system. The peak heights at the retention time of DMSO were measured and the reagent blank value was calculated to be at .006 ppm.

Duplicate samples of milk fortified prior to extraction with methanol at zero, 0.1 and 0.2 ppm and the liver fortified at 0.2 and 0.4 ppm of DMSO (in methanol) and aliquots equivalent to 30g were taken through the procedure. The samples were made to final volume of 1.0 ml in methanol and suitable aliquots were injected in the GLC system and compared to DMSO standards run concurrently. The background for both milk and liver samples was excellent. The check samples for milk had apparent residue equivalent to 0.06 and 0.04 ppm of DMSO and liver samples equivalent to 0.1 and .09 ppm of DMSO. In addition to this, all the milk and liver samples (including untreated checks) recorded a large and overscale peak at the retention time of 8 minutes. A standard of dimethyl sulfone was injected and gave a peak at the same retention time of 8 minutes. Dimethyl sulfone may be a contaminant or metabolite in all the samples.

Further work should show if the dimethyl sulfone occurs naturally in meat and milk. Our results for milk and liver obtained at Camas, Washington, using the Teflon column packed with 20% FFAP are:

A. Milk

<u>Sample No.</u>	<u>ppm DMSO added</u>	<u>ppm DMSO found</u>	<u>net residue</u>	<u>% Recovery</u>
1	none	.06	---	---
2	none	.04	Av. .05	
3	0.1	.12	.07	70%
4	0.1	.12	.07	70%
5	0.2	.183	.133	67%
6	0.2	.19	.14	70%

B. Beef liver

1	none	0.1		
2	none	0.09	Av. .095	
3	0.4	0.52	.425	106%
4	0.4	0.5	.405	101%
5	0.2	0.33	.235	117%
6	0.2	0.30	.205	103%

The total time spent at Crown Zellerbach was 9 working days.

Conclusion:

The simple and rapid method developed by us may be used for the determination of residues of DMSO in milk, beef liver, lettuce and soybeans at the proposed tolerance levels. No precautions are necessary to avoid the exposure of samples to air. The method developed by us is superior to that submitted by Crown Zellerbach and can be completed in one day.



Gobind P. Makhijani

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Pesticide Petition 4F1486

16 DEC 1976

Mr. J. A. Chapman
Crown Zellerbach Corp.
Camas Washington
98607

Dear Mr. Chapman:

We are unable to act favorably on your request to expand the present exemption for dimethyl sulfoxide to include use as a solvent or cosolvent within 1 day of harvest. The question of potentiation between DMSO and other chemicals precludes further exemption. We believe that tolerance proposals for DMSO would be necessary to support each combination; ie. DMSO + parathion in wheat. Sufficient information would be required to support the proposals for DMSO and to show that established tolerances for the individual pesticide would not be exceeded.

Sincerely,

Richard F. Mountfort *RFm*
Product Manager (23)
Fungicide-Herbicide Branch
Registration Division (WH-567)

WH-567:FHB:RFMountfort:mmq:rm351 WSME,x51397:12/10/76

? The week of Dec 6 G. Mahbuzani was sent to petitioner's lab to do a method trial ??? Who made chue decision?

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CB

5

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

SUBJECT: PP #4F1486 - DMSO; exemption from the requirements of a tolerance with a 24 hour PHI pursuant to 40 CFR 180.1001(d).

DATE: OCT 14 1976

Crown Zellerbach letter of 8/16/76 (J. A. Chapman).

Received on TB: 9/16/76

Assigned to AT: 1600 hours 9/17/76

Related Petitions: 1E1017; 3E1364

FROM: D. Ritter, TB

Dan Ritter 10/1/76
2. for CEC 10/13/76

TO: PSO and CHM, PM #23

We will address each point individually as it appears in the letter.

Crown Zellerbach (CZ):

Mr. Chapman takes exception to the way RD has handled the DMSO petitions. He states that, the exemption having passed scientific scrutiny, he now learns that tolerances are being contemplated, representing a shift in Division policy.

TB Reply:

He is correct. We spoke to R. Mountfort (PM #23) who had personally called Chapman to this effect.

CZ:

Company first sought inert status in 1970, and over the years have submitted or referenced data "far" in excess of that normally required for inerts.

TB Reply:

This is essentially true. The first DMSO petition (PP #1E1017) contains a comprehensive summary of relevant TOX data (review of R. P. Schmidt, 12/16/71). Some pertinent points in that review include:

- 2 -

<u>Species</u>	<u>Duration</u>	<u>Route</u>	<u>NEL</u>	<u>Toxic Signs</u>
Monkey	100 day	gavage	5 Gm/kg	none
Swine	26 weeks	eye	1.5 Gm/kg	none
Dog*	8 months	gavage	5 Gm/kg	none
Monkey	18 months	gavage	3 Gm/kg	none
"	18 months	dermal	3 Gm/kg	scaling initially

*An unusual eye effect was noted but could not be evaluated as to actual hazard.

Comparative studies of the relative toxicities of various other solvents were done, as was one study that compared the acute oral LD₅₀'s of five major pesticides (thiram, dieldrin, parathion, carbaryl and MC-A-600) in combination with DMSO, aqueous suspension and corn oil. Neither study showed enhancement or reduction in toxicity due to DMSO.

Several teratology studies proved negative in mammals and showed positive in chick embryos at huge doses.

One eighteen month rat tumor study showed evidence that DMSO ^{elicited} ~~eliated~~ a reduction in tumor incidence when compared to controls.

Several sophisticated studies revealed that DMSO neither increases or decreases the incidence of pre-existing tumors.

DMSO was cleared eventually under 40 CFR 180.1001(d) with a 1 lb./acre limitation, intended for soybeans and corn only and restricted to pre-emergent application only.

CZ:

Company is concerned that some toxic materials have been cleared as inerts without limitation, and that these could be present in rats at levels equal to or greater than DMSO.

- 3 -

TB Reply:

Chapman is correct, of course. Methanol has unrestricted use in (d) for example. But we were pretty sure about its toxicity profile which was not the case with DMSO. Moreover, socio-political considerations* were operative in the TOX deliberations that dictated the utmost caution. These concerns have now been adequately addressed (e.g., see D. Ritter review of 10/16/75, PP #4F1468).

CZ:

"...DMSO is one of the least toxic solvents currently on the exempt list." Recent human ingestion studies show no toxic effect at 100 mg/kg/five day week for seven weeks followed by an additional seven week exposure of 500 mg/kg/five day week.

TB Reply:

1. ...least toxic solvent... - DMSO is less toxic than xylene, toluene and benzene but it's more toxic than water and ethanol.
2. Human ingestion - TB has heard of, but has not seen, these studies. The results, if true, are not surprising in light of work presented in dog and monkey studies.

CZ:

Establish tolerances instead of exemption when not required of other inerts in the basis that it is an economic poison (EP).

TB Reply:

Technically, all materials used in pesticide formulations are EPs; what he means is that it is considered an active ingredient (AI). DMSO in particular was declared an AI in the 6/6/68 memo of Harry W. Hayes; PRD/ARS/USDA.

*Refers to much publicity in laypress and some in popular scientific publications.

- 4 -

In D. Ritter's review of 9/9/74, PP #4F1468, TB recommended the tolerance route and the 24 hour PHI, citing the AI status as well as our concern for the potential for enhanced activity of the pesticides being used with DMSO. We cited our concern that established tolerances for pesticides used with DMSO might need re-examination in light of the propensity of DMSO to enhance translocation of other materials across all walls (foliar application, for example).

A meeting with CZ was held 1/23/75 (see R. Beyak memo of conference, PP #4F1468) and our major concern as to potentiation of pesticide was alleviated by agreeing that this could be handled at the time of registration. Subsequently, TB decided tolerances would not be needed for residues of DMSO per se (G. E. Whitmore and D. Ritter). }

As to the question of comparing the handling of DMSO with that of other inerts, TB will always consider each case on its individual merits, taking due account of all relevant data and administrative questions.

CZ:

...safety factors of 18,000 to 119,000 based on animal and human data...

TB Reply:

The upper limit is probably high; not having seen the human data we cannot comment. But using the long term monkey results, 18,000 is in the right ball park.

There really is no hazard, overall, from the proposed use.

CZ:

24 hour PHI would be dropped since pesticides are not applied after this.

TB Reply:

We believe some crops that ripen at different times such as citrus, pome fruits, etc. may be sprayed at any time right up to harvest. In fact, there is concern at OSHA concerning re-entry data for field workers, and we understand this deals with intervals less than 24

- 5 -

hours. We therefore conclude that the 24 hour PHI should remain, if use pattern alone is considered. This is not to say that any residues remaining after a period of less than 24 hours would be a hazard.

CZ:

A meeting is proposed.

TB Reply:

we will meet at a time agreeable to all.

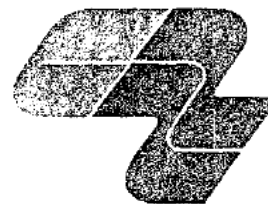
Note: TB is still of the opinion that an exemption from the requirement of a tolerance is appropriate for DMSO and therefore reiterates our conclusions of 10/16/75 and of 11/25/75, D. L. Ritter.

However, if for other than scientific reasons tolerances are deemed appropriate, the Toxicity data in hand will support those tolerances proposed in the CB review of 7/29/76, R. J. Hummel.

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pp* 481486

CrownZellerbach
Chemical Products Division



Registered Mail.
Return Receipt Requested

August 16, 1976

Mr. John R. Ritch, Jr., Director
Registration Division
United States Environmental Protection Agency
Waterside Mall East Tower
Washington, D.C. 20460

Dear Mr. Ritch:

We strongly object to the way your Division is handling our Petition 4F1486, in which we have requested amendment of the exemption status on dimethyl sulfoxide (DMSO) as a pesticide solvent. After we had been advised that the petition passed your scientific review and evaluation, we were recently told that DMSO may no longer be viewed as an exempt solvent because of a possible change in your Division's policy.

Since 1970, when we began seeking exemption from tolerance for DMSO, we have carefully conducted residue studies and gathered together a great deal of toxicological data, following advice and consultation with your staff. Your people have indicated the amount of information submitted far exceeds the norm for an inert ingredient.

It has been very frustrating to us that during the past five years of working with your Division we have seen inert ingredients much more toxic than DMSO placed on the exempt list with no use limitations. I have attached a partial list of those having vapor pressures similar to or less than DMSO which would indicate their presence on food crops would be similar to or greater than that of DMSO.

We can state unequivocally DMSO is one of the least toxic solvents currently on the exempt list. For example, it has approximately the oral toxicity of glycerine and is far less toxic than any of the exempted alcohols or ketones. DMSO has been studied with eight species of animals, including humans, as well as many fish and birds. One of the most recent studies involved humans orally receiving 100 mg. of DMSO per kilogram of body weight, five times per week for seven weeks, plus 500 mg per kilogram daily for an additional seven weeks with no toxic side effects.

We were recently advised that our petition has been held up because of possible changes in the Division's position on inert ingredients -- that of establishing tolerance levels for those with time of application

Mr. John R. Ritch, Jr.

-2-

August 16, 1976

limitations. This would be highly undesirable in the case of DMSO from two major standpoints. First, it would in effect place DMSO outside of the list of inert ingredients into the same category as active ingredients. This, in essence, would classify DMSO as an economic poison under FIFRA. This would be improper since DMSO is inert as a solvent and since we are not attempting to register DMSO as an economic poison. Secondly, it would cast DMSO in an unfavorable light with pesticide firms. In addition to the work of determining residues of their active ingredients, the firms would have to concern themselves with residues of DMSO before registration petitions could be fully developed. Since this extra burden is not required with other solvents, the benefits of using DMSO would have to be enormous to justify its use in formulations.

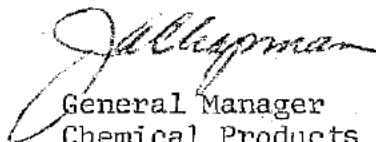
We can fully appreciate the need for tighter control of inert ingredients. Some of them have toxicities approaching those of registered pesticides.

However, we do not understand the Division's position with respect to DMSO. Our studies of residue and toxicity data show large factors of safety between amounts that could be expected to be retained on crops and those that would be toxicologically significant. Our last petition suggests the safety factors could be in the range of 18,000 to 119,000. These were calculated from long term feeding studies on Rhesus monkey and humans.

In petition 4Fl486 we suggested amending the current exemption to allow application up to within 24 hours of harvest. This was not suggested for toxicological reasons but because this appeared to be the shortest commercially feasible period between application of a pesticide and harvest of a crop. Therefore, we felt this would give the maximum residues of DMSO that would ever occur, and our studies were conducted in accordance with this concept. If the problem of giving DMSO an exemption from tolerance status lies with this self-imposed time limit, perhaps it would be best to eliminate this limit entirely. This would not increase the chances of higher residues since it is inconceivable that pesticide formulations would be applied to growing crops within any shorter period than 24 hours.

In any event, I would like you to review this matter and would appreciate a meeting with you at your earliest convenience to explore it in more detail.

Very truly yours,



General Manager
Chemical Products Division

J. A. CHAPMAN/hw

Attachment

INERT INGREDIENTS APPROVED UNDER 180.1001 (c) or (d) WITHOUT LIMITS

180.1001 (c)

<u>Compound</u>	<u>Use</u>	<u>Oral LD50, rat</u>	<u>Normal Boiling Pt.</u>	<u>Comments</u>
Ammonium Carbamate	Synergist	39 mg/kg (IV)	Non-volatile	Approved 1/3/74
Ammonium Hydroxide	Solvent	350 mg/kg	Non-volatile	--
Benzoic Acid	Preservative	2370 mg/kg	249°C	--
Oleic Acid	Diluent	230 mg/kg (IV mus)	286°C	Reapproved 6/2/74
Sodium Sulfite	Stabilizer	57 mg/kg (TDLo-humans)	Non-volatile	Approved 11/18/7
Lactic Acid	Solvent	3730 mg/kg	Non-volatile	Approved 10/21/74
Rhodamine B	Dye	500 mg/kg (rat LDLo)	Non-volatile	Approved 10/21/74

180.1001 (d)

Acrylic Acid polymerized	Surfactant	340 mg/kg	Non-volatile	Approved 1/20/70
Boric Acid	Sequestrant	2660 mg/kg	Non-volatile	Reapproved 1971
n-Decyl Alcohol	Solvent	4720 mg/kg	231°C	Reapproved 2/9/72
Methyl Isoamyl Alcohol	Solvent	4760 mg/kg	144°C	Approved 1/3/74
Phenol	Solvent	414 mg/kg	182°C	Reapproved 1971
Ethylene glycol monobutyl ether	Solvent	1480 mg/kg	171°C	Reapproved 6/1/70
n-Hexyl Alcohol	Solvent	4590 mg/kg	157°C	Reapproved 2/9/72
Tetrahydrofurfuryl Alcohol	Solvent	2500 mg/kg	178°C	Approved 3/25/74
Methyl Isobutyl Alcohol	Solvent	2160 mg/kg	124.3°C	Approved 11/18/74
Terephthalic Acid	Plasticizer	1900 mg/kg (IV mus)	Sublimes 300°C	Approved 11/18/7
Ethylene Glycol Monomethyl ether	Solvent	2460 mg/kg	124°C	Approved 11/18/74
Zinc Sulfate	Diluent, carrier	40 mg/kg (Ipr-rat)	Non-volatile	Approved 10/21/74
Sodium molybdate	Nutrient	344 mg/kg (Ipr-mus)	Non-volatile	Approved 2/2/76
Cyclohexanol	Solvent	2060 mg/kg	161.5°C	Approved 2/2/76
Cyclohexanone	Solvent	1620 mg/kg	156.7°C	Approved prior to 1974

Comparison

Dimethyl Sulfoxide (DMSO)	Solvent	17400 to 28300 mg/kg	189°C
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PP# 4F1486

JUN 17 1976

PP# 4F1486. Method tryout request for DMSO

R. J. Hummel, Chemist
Chemistry Branch, RD

R. W. Storcherr, Analytical Methods Section
Chemistry Branch, RD

THRU: Joseph G. Cummings, Chief
Chemistry Branch, RD

You are requested to conduct a tryout of the petitioner's analytical procedure for DMSO in plant tissue. Soybeans and lettuce are to be fortified with DMSO at a level of 10 ppm. Blanks and recoveries are to be run in duplicate.

You are also requested to determine whether this procedure or a modified version of this procedure would be adequate to enforce tolerances in meat and milk. Beef liver is to be fortified with DMSO at levels of 0.2 and 0.4 ppm and milk, at levels of 0.05 and 0.1 ppm. Blanks and recoveries are to be run in duplicate.

No residue data were obtained using this method. Thus, you are free to make any changes in the procedure which you feel may be beneficial. As written, the method appears rather tedious as continuous care is taken to avoid exposure of the sample to air. It is possible that the high control values and the recoveries greater than 100% reported by the petitioner are due to contamination of the air in his laboratory with DMSO. Thus, many of the precautions he takes may be unnecessary. In addition, you may wish to substitute more sensitive detectors for the flame ionization detector used by the petitioner.

A copy of the petitioner's method including all pertinent data is attached. Please return this material as it is part of the PP#1E1017 and is needed in our files. You have indicated (telecon, R. Hummel/R. Storcherr, 5/10/76) that samples of DMSO suitable for use in this tryout are available.

This tryout has been given the highest priority and should be initiated immediately. Please inform us of your results as soon as possible.

R. J. Hummel

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Petition

PP# 471486. Proposed exemption for dimethyl sulfoxide (DMSO).

R. J. Hummel, Chemist
Chemistry Branch, RD

PM 23 (R. Mountfort) and Toxicology Branch

THRU: Chief, Chemistry Branch

The Registration Division is considering establishing tolerances for residues of DMSO resulting from its use as a solvent or cosolvent. Restrictions are proposed against use within 24 hr. of harvest and against post-emergence use on crops which may be used for grazing, forage, silage or fodder.

Areas of Consideration
Analytical Method

A flame ionization GLC method for determining GLC residues on crops was submitted in connection with PP# 1E1017. The method appears rather tedious as continuous care must be taken that the sample is not exposed to the air. At least in the petitioner's laboratory, the air contained a substance which interfered with DMSO determinations.

Using this method, recoveries from corn plants (mixture of leaves, stems and grain) at DMSO fortification levels of 5, 10, 20 and 100 ppm ranged from 72-160%. Untreated samples contained apparent DMSO residues of 1-3 ppm. The high recovery values are obtained primarily at the lower fortification levels and are apparently due to exposure of the samples to contaminants in the air. It could be speculated that the high recoveries and control values are due to contamination of the air in the petitioner's laboratory with DMSO. Thus, the results of a HQ in our laboratory would give a better indication of the potential sensitivity of this method.

No confirmatory method has been submitted. In order to conclude that adequate methods are available for the enforcement of tolerances, we will require either a confirmatory method or data showing that registered pesticides do not interfere with analyses for DMSO.

No analytical methods for determining DMSO residues in meat, milk, poultry and eggs have been submitted. In order to establish tolerances on these commodities, adequately validated analytical methods are needed.

In order to establish tolerances for residues of DMSO, we will require an adequately validated analytical method for meat, milk, poultry and eggs and either a confirmatory method or data showing that pesticides with established tolerances do not interfere with DMSO analytes. Successful method tryouts on crops, meat, and milk would also be needed.

X

PP# 471486

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Residue Data

Residue data for representative crops were obtained using radio chemical techniques. These data indicate that DMSO residues resulting from the proposed use will not exceed 2 ppm in the edible portions of fruits and vegetables and 6 ppm in grains. No residue data for representative forage items were submitted; consequently, DMSO is limited to pre-emergence use on crops with forage items. Pre-emergence use on forage grasses and forage legumes at 11b/A resulted in DMSO residues of 0.01-0.03 ppm.

In view of the limited number of crops for which residue data are available, we would recommend that any tolerance for DMSO residues on crops be established at a level of 10 ppm. This is approximately twice the highest level found in the above residue studies and will give a margin of safety to cover possible residue variability in other crops and other climatic conditions.

Meat, Milk, Poultry and Eggs

A goat and 3 chickens were fed ³⁵S-DMSO at a level of 20 ppm in the total solid diet for 28 days and sacrificed 24 hr. after the last dose. Analyses by radioisotopic techniques indicated maximum DMSO residues of 0.06 ppm in milk, 0.28 ppm in eggs, 0.2 ppm in goat tissues (liver) and 0.44 in chicken tissues (liver).

Thus, a diet containing 10 ppm DMSO would result in maximum DMSO residues of ca. 0.05 ppm in milk and ca. 0.2 ppm in eggs and tissue. Any tolerances for DMSO residues in meat, milk, poultry and eggs should be established at these levels.

Recommendations

If it were deemed advisable to establish tolerances for DMSO residues, we would suggest the following levels:

- 10 ppm in or on crops
- 0.2 ppm in eggs and the meat, fat and meat byproducts of cattle, goats, hogs, horses, and sheep
- 0.05 ppm in milk poultry

However, prior to establishing tolerances for DMSO residues, we will require the following:

1. An adequately validated analytical method for determining DMSO residues in meat, milk, poultry and eggs. This method should be sensitive to 0.05 ppm in milk and 0.2 ppm in eggs and tissue.

3

2. Either a confirmatory method or data showing that pesticides with established tolerances do not interfere with DMSO analyses.
3. Successful method tryouts of the analytical methods for determining DMSO residues in crops and meat, milk, poultry and eggs.

K. J. Hummel, Ph.D.

cc: TOX, EHE, FDA, CHM(5)

WH-567:RJH:JHE:mer:Bm 108:WSE:EX62610:6/21/76

RDE:JGC:WINGS:6/14/76

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PP# 4F1486

PP#4F1486. Proposed exemption for dimethyl
sulfoxide (DMSO). Amendment of 11/3/75.

APR 9 1976

R. J. Nussel, Chemist, Chemistry Branch, Registration Division (MS-567)

Product Manager 23 (R. Mountfort) and Toxicology Branch

THRU: Chief, Chemistry Branch.

In the reject letter of 10/17/75 (see memo of R. F. Mountfort), the petitioner was informed that for a favorable recommendation, we would require residue data for representative forage items such as alfalfa, clover, corn forage and soybean forage. In response, the petitioner proposed the following limitation on use of DMSO: "Not to be applied within 24 hr. of harvest. Not to be applied after formation of edible parts of grasses or forage crops grown for grazing, fodder or silage."

The petitioner was informed (see memo of telecon, R. F. Mountfort/J.A. Chapman, 11/20/75) that the restriction against application to grasses or forage crops after the formation of edible parts was not appropriate as the whole aerial portions of these crops are edible. In accordance with our suggestion, the petitioner has revised his use limitations and now proposes the following: "Not to be applied within 24 hours of harvest. Not to be applied to crops which may be used for grazing, forage, silage or fodder after emergence from soil."

In our previous review (see memo of Dr. R. J. Nussel, 9/16/75), we reported the levels of residues in meat, milk, poultry and eggs resulting from the feeding of 20 ppm DMSO. However, we were unable to give an estimate of residues resulting from the proposed use as there were no residue data for representative forage items.

With the above restriction against postemergent applications to crops which are grazed or foraged, the major source of DMSO residues in the livestock diet will be grains. These may contain ca. 5 ppm DMSO. IOI has previously concluded that residues in meat, milk, poultry and eggs resulting from the feeding of 20 ppm DMSO are safe (see memo of C. Witter, 10/16/75).

We conclude that residues in meat, milk, poultry and eggs resulting from the proposed use will not exceed levels previously considered safe by IOI. Thus, the only deficiency in the petition has been resolved.

Other Considerations

In connection with a recent request for an exemption for epichlorohydrin, we commented (PP#5E1384, memo of J. C. Cummings, 12/10/75) that suggestions

-2-

are probably not appropriate for inertis when the safety is based on a controlled use pattern. Although the use pattern for DMSO is also limited, TOX has informed us (G. Ritter, personal communication, 3/2/76) that, in contrast to epichlorohydrin, there is a substantial amount of toxicity data available for DMSO. Even expected initial residues of DMSO on crops (ca. 100 ppm) would not be hazardous. Since the question of safety on residues is not involved, we do not believe this favorable recommendation for DMSO is in conflict with our position on epichlorohydrin.

Recommendation

TOX states (memo 11/20/75) that CHM considerations permitting, they can recommend that DMSO be exempted under 180.1001(d). Therefore, we recommend that the proposed exemption for dimethyl sulfoxide be granted. Section 180.1001(d) should be amended to read as follows:

<u>Inert ingredients</u>	<u>Limit</u>	<u>Uses</u>
Dimethyl sulfoxide	Not to be applied within 24 hours of harvest. Not to be applied to crops which may be used for grazing, forage, silage or fodder after emergence from soil.	Solvent, cosolvent

CC: TOX, EEE, WFO-136(FOA) CHM (5)
 WH-667:CHM:R.S. HUMMEL:bel:MSME:X62612(3/27/76)
 RGI:R.S. QUICK:3/4/76:J.G. CUMMINGS:3/11/76

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CB

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

SUBJECT: PP # 4F1486; DMSO exemption from the requirements of a tolerance pursuant to 40 CFR 180.0110(d) with limitations. Amendment of 10/27/75

NOV 25 1975

FROM:

Toxicology Branch

TO:

R. F. Mountfort, PM #23
Chemistry Branch

DATE: *[Signature]*
[Signature]
H 1486

Crown Zellerbach Corp.
Camas, Washington

Petitioner submits an amendment to his original request for exemption of DMSO from tolerances. This limits use to (d), preharvest application only, with a 24 hour PHI restriction and a restriction concerning formation of edible parts of grasses or forage crops grown for grazing, fodder and silage.

This grazing restriction is proposed in lieu of residue data on representative forage crops needed by CB in order to determine possible residues in meat, eggs and milk.

Otherwise, the safety of DMSO from the proposed use is defined (see my review of 10/16/75).

Recommendation:

TB has no objection to exempting DMSO under (d) with the above restrictions provided CB concurs.

David L. Ritter 12/18/75

David L. Ritter, Toxicologist
Toxicology Branch OEP 11/24/75

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CrownZellerbach
Chemical Products Division

90 day
2-23-76



November 20, 1975

Registration Division (WH-567)
United States Environmental
Protection Agency
Washington, D.C. 20460

Attn: Mr. Richard F. Mountfort
Product Manager (23)
Fungicide-Herbicide Branch

Gentlemen:

Re: Pesticide Petition No. 4F1486

In reference to our discussion of November 20, we are agreeable to and hereby apply for amendment of 180.1001(d) to permit the use of dimethyl sulfoxide as follows:

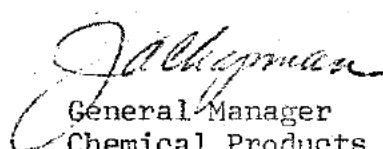
Use: Solvent, cosolvent

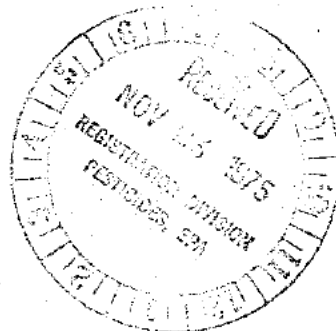
Limits: Not to be applied within 24 hours of harvest.

Not to be applied to crops which may be used for grazing, forage, silage or fodder after emergence from soil.

Very truly yours,

J. A CHAPMAN/hw


General Manager
Chemical Products Division



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of
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Rev'd CEM
9 NOV 1975

Pesticide Petition No. 4F1486

Mr. J. A. Chapman
Crown Zellerbach
Chemical Products Division
Camas, Washington 98607

Dear Mr. Chapman:

We have received your letter of October 27, 1975 concerning Pesticide Petition No. 4F1486 which now proposes that §180.1001(d) be amended regarding uses and limits of dimethyl sulfoxide, as follows:

Uses: Solvent, cosolvent

Limits: Not to be applied within
24 hours of harvest.
Not to be applied after
formation of edible parts
of grasses or forage crops
grown for grazing, fodder
or silage.

This petition is considered amended as of November 3, 1975, the date we received your letter. We have referred this amendment to our scientific staff for evaluation and comment. Further action awaits completion of their review.

Sincerely,

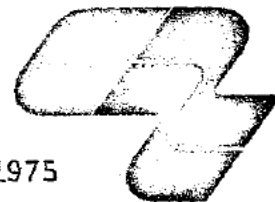
Richard F. Mountfort *RFM*
Product Manager (23)
Fungicide-Herbicide Branch
Registration Division (WH-567)

WH-567:FHB:RFMountfort:mmq:rm351 WSME,x51397:11/6/75

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of
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CrownZellerbach
Chemical Products Division

October 27, 1975



Mr. Richard F. Mountfort
Product Manager (23)
Fungicide-Herbicide Branch
Registration Division (WH-567)
UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
Washington, D.C. 20460

Dear Mr. Mountfort:

Re: Pesticide Petition No. 4F1486

You stated in your October 17 letter that you cannot act favorably on the petition because the lack of residue data on representative forage crops precludes correlation with levels of total residues in meat, milk, poultry and eggs.

As your notes may indicate, this point was discussed during our meeting on January 23, 1975 and we stated that if after the second review this still presents a problem, we would add further limitations on the use of dimethyl sulfoxide.

To eliminate the problem completely, we are agreeable to the amendment of 180.1001(d) to permit the use of dimethyl sulfoxide as follows:

Uses: Solvent, cosolvent.

Limits: Not to be applied within 24 hours of harvest.
Not to be applied after formation of edible parts of grasses or forage crops grown for grazing, fodder or silage.

These limitations are consistent with our data and your previous conclusions.

Very truly yours,

General Manager
Chemical Products Division

J. A. CHAPMAN/dp

11-11-75

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of
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Rcvd CHM

OCT 16 1975

17 OCT 1975

#1486

Pesticide Petition No. 4F1486

Mr. J.A. Chapman
Crown Zellerbach
Chemical Products Division
Camas, Washington 98607

Dear Mr. Chapman:

This refers to Pesticide Petition No. 4F1486 proposing the amendment of §180.1001(d) to permit the use of dimethyl sulfoxide as follows:

Uses: Solvent, cosolvent

Limits: Not to be applied within 24
hours of harvest.
Not to be applied to pasture
or range grasses grown for
grazing after soil emergence.

We have completed our review of this petition and find that we cannot act favorably on it for the following reasons:

1. In order to determine the levels of total residues in meat, milk, poultry and eggs, we will need residue data for representative forage items such as alfalfa, clover, corn forage and soybean forage. Refer to our previous correspondence, specifically December 2 and August 2, 1974. We interpret the data for peas and soybeans as originally submitted, to represent analysis of the bean or pea only, not the forage.

Sincerely,

Richard F. Mountfort *RFM*
Product Manager (23)
Fungicide-Herbicide Branch
Registration Division (WH-567)

WH-567:FHB:RFMountfort:mmq:rm351 WSME,x51397:10/16/75

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY CBRevd ~~CHM~~

OCT 16 1975

SUBJECT: PP#4F1486; DMSO, Dimethyl sulfoxide, exemption
 from the requirements of a tolerance, CB review of 9/16/75,
 R.J. Hummel, amendment of 5/16/75.

DATE: OCT 16 1975

FROM: TB

TO: R. Mountfort, PM# 23
 and Chemistry Branch

Crown Zellerbach
 Canas, Wash.

Related Petitions
 1E1017 3E1364

This review is in response to additional CB data requested in
 COB reject letters of 8/24/74 and 12/2/74, L. Zink, CB has
 concluded:

1. Maximum DMSO residues from exaggerated feeding studies will
 be 0.06 ppm in milk and 0.2 - 0.44 ppm maximum in flesh. The
 remaining residues are unidentified components thought to be at
 least partly incorporated into normal tissue constituents; CB
 defers to TB the need for further characterization of these.

TB Response: We can accept these levels since the toxicology
 of DMSO is well documented and its safety by oral ingestion has
 been demonstrated (see review of 12/16/71 R.D. Schmidt PP# 1E1017).
 Since DMSO is residue of toxicological concern, we do not now feel
 that further characterization of these unidentified components in
 meat, milk, poultry and eggs is needed.

2. Residues in edible portions of fruit will not exceed 2 ppm;
 in the grain the maximum will be 6 ppm.

TB Response: We do not consider these to be unsafe levels in
 light of (1) above - safety by oral ingestion.

3. CB will require data on representative forage items in order to
 determine total residues in meat and milk.

TB Response: Such information is needed to permit a final
 judgment as to the safety of secondary residues.

2.

4. CB will require an analytical method since tolerances were needed.

TB Response: In our previous review of 9/9/74, D.L. Ritter, we concluded that DMSO was an "active ingredient", and that tolerances would be needed. However, although DMSO's unique solvent properties might enhance pesticidal activity, there would be no label claim for direct pesticidal action of DMSO per se; hence DMSO would qualify as an "inert ingredient" within the meaning of 40 CFR 180.1001, and TB henceforth will consider it as such.

Therefore, an analytical method should not now be needed.

7
CB determination

CB concludes, and TB concurs, that TB questions of potentiation of active materials by DMSO can be handled at the time of registration of the formulation.

Conclusions

Overall we conclude that our major concerns (see review of 9/9/74, D.L. Ritter) are satisfied and we can clear DMSO as a solvent; co-solvent in 180.1001 (d) with a 24 hour PHI, CB considerations permitting, provided petitioner supplies CB with the forage residue data needed to determine a level in meat, milk, poultry and eggs.

Recommendations:

Contingent upon receipt of satisfactory CB data and a favorable CB recommendation, we tentatively recommend that an exemption from the requirements of a tolerance for Dimethyl-sulfoxide be established pursuant to 40 CFR 180.1001 (d) with a 24 hour PHI restriction. The use is as a solvent; cosolvent.

David L. Ritter 10/15/75
David L. Ritter, Adjuvants Toxicologist
Toxicology Branch
Registration Division

cc: Branch File:CB:EEEB:PP# 4F1486

Init: O.E. Paynter 10/14/75

Initial: O.E. Paynter

DLRitter:gac 10/14/75

OEP 10/15/75

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of
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#1486

SEP 16 1975

PP# 4F1486. Proposed Exemption for Dimethyl-sulfoxide. Amendment of 5/16/75

R. J. Hummel, Chemist, Chemistry Branch
Registration Division (WH-567)

Product Manager 23 (R. Mountfort),
Toxicology Branch and R. Ney

THRU: Chief, Chemistry Branch

THRU: Petitions Control Officer

In our previous evaluations of this petition (see memos of R. Bayak, 7/24/74 and 10/24/74), several deficiencies were cited. In response, the petitioner has submitted additional analytical data, a bovine metabolism study and a discussion on potentiation of pesticide residues by DMSO. The deficiencies, as listed in the COB reject letters of 8/2/74 and 12/2/74 (L. A. Zink), the petitioner's comments and our responses are given below:

1. We need to know the composition of the residue as determined by total ^{35}S activity, in milk, eggs, and meat tissues (excluding fat and goat liver) from the ingestion of ^{35}S -labeled dimethyl sulfoxide; based on these results, we may require further identification of uncharacterized residues in these items.

The petitioner has submitted all the raw and analytical data obtained from the goat and chicken feeding studies discussed in our original review. In these studies, a goat and 3 chickens were fed ^{35}S -labeled DMSO at a level of 20 ppm in the total solid diet for 28 days and sacrificed 24 hours after the last dose. Eggs and milk were sampled throughout the feeding period; analyses of these by the radiochemical techniques discussed in our original review indicated that total ^{35}S activity plateaued rapidly. The following results are reported:

Commodity	Total ^{35}S Activity	DMSO		DMSO ₂		Unidentified Extractable Activity		Non-Extractable Activity	
	ppm	ppm	%*	ppm	%*	ppm	%*	ppm	%*
milk	0.49-0.64	.02-.06	6**	.1-.18	25**	.08-.2	30**	.13-.29	39*
eggs	1.24-3.00	.15-.26	12**	.11-1.55	35**	.42-.86	31**	.15-.53	22**
goat liver	3.85	0.2	5	0.22	6	0.82	21	2.62	68
goat kidney	2.21	0.09	4	0.18	8	0.83	36	1.11	50
goat muscle	0.69	0.06	9	0.08	12	0.13	19	0.41	59
goat fat	0.46	<0.01	<2	<0.01	<2	0.02	4	0.43	93
chicken liver	2.13	0.44	21	0.32	15	0.75	35	0.62	29
chicken muscle	1.31	0.20	15	0.35	27	0.36	27	0.39	30
chicken fat	0.42	<0.01	<2	<0.01	<2	0.01	2	0.41	98

*% of total ^{35}S activity

**average of 4 analyses

-2-

The petitioner has also submitted a copy of the experimental work done by Dr. Jochle, *et al.*, of Syntex on the bovine metabolism of DMSO. Cows and calves were given (either topically, subcutaneously or intramammarily) a single dose of ca. 5-10g. ^{14}C -labeled DMSO. Milk, excreta and expired air were monitored for total activity. Urine was analyzed for DMSO and DMSO_2 ; activity in milk, feces and expired air was not characterized.

Similar elimination routes were observed for all 3 types of application. Activity was eliminated largely in the expired air (presumable as dimethyl sulfide (DMS)) and urine; ca 2% of an intramammary dose was eliminated in milk. Urinary activity was comprised largely of DMSO for the first 20 hours after application; thereafter, it was comprised solely of DMSO_2 . After DMSO disappeared from the urine, no more ^{14}C activity was eliminated in the expired air. Since DMS can be formed from DMSO but not from DMSO_2 , this would indicate that after 20 hours all circulating DMSO has been metabolized to DMSO_2 . It is noted in this paper that both meat and milk always contain DMS and/or DMSO_2 in appreciable amounts.

In summary, the feeding of 20 ppm DMSO in the diet leads to relatively high levels of total residues in meat, milk, poultry and eggs. Depending upon the commodity, the ^{35}S activity identified as either DMSO or DMSO_2 ranges from less than 4% in beef and goat tissues to ca. 50% in eggs; the majority of residues in milk, eggs and tissues consists of either non-extractable metabolites or unidentified extractable metabolites. The available animal metabolism data indicate that DMSO is extensively metabolized to both DMS and DMSO_2 . These two compounds are part of the animal's endogenous sulfur pool and are available for further biosynthesis. Thus, it is possible that the majority of unidentifiable and non-extractable ^{35}S activity in the above DMSO feeding studies is due to incorporation of ^{35}S into sulfur containing natural constituents such as proteins.

We defer to TOX as to whether additional characterization of the residues in meat, milk, poultry and eggs is needed. Since residue data for forage items have not been submitted (see Deficiency 3), we are unable to gauge the levels of total residues in meat, milk, poultry and eggs resulting from the proposed use.

2. We need to know the details of the sample preparation techniques employed for the fruit and vegetable residue studies.

The petitioner has submitted a detailed description of the procedures used to prepare crops for analysis. The procedures conform to commercial practice. Peas, dried beans and soybeans were analyzed after removal of the shell; both the lint and seed of cotton were analyzed.

-3-

We conclude that this deficiency is resolved. Although the RAC for peas is peas plus pods, the available data are adequate to support our previous conclusion that residues resulting from the proposed use will not exceed 2 ppm on the edible portions of fruits and vegetables and 6 ppm in small grains.

3. We require residue data for forage grasses; data for alfalfa and a representative pasture grass will be adequate.

No residue data for forage items are submitted. In the conference of 1/23/75 (see memo of R. Bayak), the petitioner was informed that while we did not object to the label restriction against applications of DMSO to pasture or range grasses, we would still require residue data on representative forage items. The petitioner agreed to provide us with this information. In the absence of these data, we are unable to make a conclusion concerning secondary residues in meat, milk, poultry and eggs.

We conclude that this deficiency has not been resolved.

4. We feel that the residues in fruits, vegetables, and grains represent a toxicologically significant exposure of DMSO in the human diet. Therefore, a full tolerance petition for DMSO for this proposed use (including the 24-hour preharvest interval) is required. (This petition will require a validated residue method for enforcement purposes.)

No tolerances for DMSO have been proposed. Since TOX has deemed that tolerances for residues of DMSO resulting from the proposed use are needed, validated analytical methods suitable for enforcement purposes are also needed. This deficiency remains unresolved.

5. Information or data demonstrating the effect, or lack thereof, of DMSO on the residue levels and the efficacy of pesticides and/or their metabolites on raw agricultural commodities is required.

In the conference of 1/23/75, we agreed that information on DMSO potentiation of pesticide levels should be supplied by the registrant of new formulations containing DMSO at the time of registration. Therefore this deficiency is resolved.

6. Our registration Section informs us that environmental data in support of PR Notice 70-15 will be required prior to acceptance of postemergence uses of DMSO.

EEE has informed us (R. Ney, oral communication, 8/15/75) that since DMSO is currently exempt under Section 180.1001(d) for use as a solvent in formulations applied before crop emerges from soil or prior to formation of edible parts of food plants, there is no need for soil persistence or follow-up crop data for DMSO.

-4-

Conclusions

We draw the following conclusions on the deficiencies addressed above:

1. The majority of residues in meat, milk, poultry and eggs are either non-extractable metabolites or unidentified extractable metabolites (see table in discussion of Deficiency 1 for full details). These are possibly the result of incorporation of ^{35}S into sulfur containing natural constituents. We defer to TOX as to the need for additional characterization of the residues in meat, milk, poultry and eggs. Since there are no residue data for forage items, we are unable to determine the levels of total residues in meat, milk, poultry and eggs resulting from the proposed use.
2. Adequate details of the sample preparation technique are available. We reiterate our previous conclusion that residues resulting from the proposed use will not exceed 2 ppm on the edible portions of fruits and vegetables and 6 ppm in small grains.
3. In order to determine the levels of total residues in meat, milk, poultry and eggs, we will require residue data for representative forage items such as alfalfa, clover, corn forage and soybean forage.
4. Since TOX has deemed that tolerances are needed for residues of DMSO resulting from the use proposed in this petition, validated analytical methods suitable for enforcement purposes are also needed.
5. Data on DMSO potentiation of pesticide residue levels are not needed at this time. Such data would be submitted by registrants of new formulations containing DMSO at the time of registration.
6. There is no need for soil persistence or follow-up crop data for DMSO.

Recommendations

For the reasons stated in Conclusions 1, 3, and 4, we recommend that the proposed exemption not be granted.

R. J. Hummel, Ph.D.

cc: TOX,EEE,NFO-130(FDA),CHM(5)
MH-567:CHM:RJHummel:cyf:9/18/75
RDI:RSQUICK:9/3/75,JGCummings:9/11/75

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Rec'd Mon. PM MAY 13 1975

23 MAY 1975

Crown Zellerbach
Attention: J. A. Chapman
Chemical Products Division
Camas, Washington 98607

Gentlemen:

Subject: PESTICIDE PETITION NO. 4P1486
Your letter of May 8 received May 16, 1975

We have received your certified check for \$2,000 to defray costs for review of the additional data transmitted with your letter of February 7, 1975. This petition is considered amended as of May 16, 1975, the date we received the check. Further action awaits completion of scientific review and evaluation.

Sincerely,

Richard F. Mountfort *RFM*
Product Manager (23)
Fungicide-Herbicide Branch
Registration Division (WH-567)

WH-567:FHB:RFMountfort:mmq:rm351 WSME,x51397:5/23/75

End
of
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Crown Zellerbach
Chemical Products Division

~~Received~~ MAY 13 1975

May 8, 1975

C 892458

Registration Division (WI-567)
United States Environmental
Protection Agency
Washington, D. C. 20460

Attn: Mr. Richard F. Mountford
Product Manager (23)
Fungicide-Herbicide Branch

Gentlemen:

Subject: Pesticide Petition No. 4F1486

Thank you for reconsidering our request that an additional fee not be assessed for review of material we submitted on February 7, 1975. It is unfortunate that personnel changes at your Agency preclude continuity of discussions relative to protocol on our petitions such that confusion arises as to what information is required on each submission. It appears that we are unable to resolve the controversy at hand to our satisfaction and so, in order that you may continue review of this petition, I am attaching a check in the amount of \$2,000.

As to your suggestion of submitting additional data on forage grasses at this time, we have concluded that exclusion of grasses as stated in our letter of August 8, 1974, and acknowledged in your letter of December 2, 1974, will not seriously hamper the firms now studying the possible use of dimethyl sulfoxide. Therefore, the suggested exclusion is satisfactory, and if and when interest develops, we will study grasses and submit the data under another petition. As discussed during our meeting of January 23, we would consider other exclusions if review shows them to be appropriate.

Very truly yours,

[Signature]
General Manager
Chemical Products Division

J. A. CHAPMAN/hw

Encl.

Confidential

The National Bank of Commerce of Seattle, Seattle, Washington 98124

No. 182081

19-31250

Purchaser Gordon Zellerbach

• NC/as

Date May 9, 1975

PAY TO THE
ORDER OF

San Francisco State Protection Agency

\$ **2,000.00**

San Francisco State Protection Agency

Authorized Signature

⑈ 00122081 ⑈



Commercial/financial information may be entitled to confidential treatment

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Pestic petition

14 APR 1975

Crown Zellerbach
Attention: J. A. Chapman
Chemical Products Division
Camas, Washington 98607

Gentlemen:

Subject: PESTICIDE PETITION NO. 4F1486

Your letter of April 2 received April 11, 1975

We have carefully reconsidered your request that an additional fee of \$2,000 not be assessed for review of the material submitted with your letter of February 7, 1975.

We cannot agree that this fee is not required since it is intended to defray cost of review of data, and you have presented additional data with your February 7 submission. It does not appear reasonable to argue that conferences on previous petitions could restrict information necessary to the review of this one. We do not find a record to support this contention.

In our letter of August 2, 1974, we indicated that residue data for forage grasses are required. You may wish to submit these data with the fee payment discussed above so that these data and the material submitted February 7 could be handled under the one fee.

Sincerely,

Richard F. Mountfort *RFM*
Product Manager (23)
Fungicide-Herbicide Branch
Registration Division (WH-567)

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CrownZellerbach
Chemical Products Division

April 2, 1975



Registration Division
United States Environmental
Protection Agency
Washington, D.C. 20460

Attn: Mr. Richard F. Mountfort
Product Manager (23), Fungicide-Herbicide

Dear Sirs:

Re: Pesticide Petition No. 4F1486

We have your letter of February 27 indicating you cannot begin review of the "substantive amendment" until we submit a fee of \$2,000 in compliance with § 180.33 (g).

We have examined the regulatory section referenced. We have also re-confirmed the suggestions made by the Agency during a meeting on December 7, 1972 on the type of information that should be included in subsequent petitions on DMSO filed beyond that date.

The information submitted on February 7, 1975, which was requested by the Agency during the meeting of January 23, 1975, was in our possession since petition 4F1486 was originally prepared and submitted. At the explicit request made by the Agency on December 7, 1972, this information was not included. The Agency stated at that time that maximum use of references to previous petitions be made regarding crop preparation and analytical procedures, to detail only an example and to then summarize the results on all analyses. Had we not received this request we, of course, would have included all of our technical data gathered for 4F1486 as we did on 1E1017. If you will note, we used the "example-summary" method on petition 3E1364 submitted February 23, 1973, and this was acceptable with the Agency at that time.

For the foregoing reasons, we conclude that the information submitted on February 7, 1975 does not constitute a substantive amendment nor, under the circumstances, we should be obligated to remit any additional fee. We ask that your request for submission of the fee be withdrawn and that your review begin promptly so that we might have a determination as early as possible.

Very truly yours,

J. A. CHAPMAN, Jr.

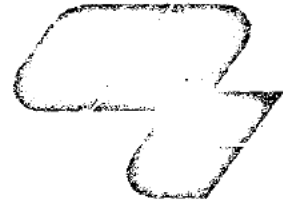
General Manager

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CrownZellerbach

Chemical Products Division

February 7, 1975



Registration Division
 United States Environmental
 Protection Agency
 Washington, D. C. 20460

Gentlemen:

C 892445

Re: Pesticide Petition No. 4F1486

In accordance with our meeting of January 23, 1975, we have attached the following information that you felt would be helpful in the review of the above petition:

1. For better clarification of our work with food crops a description of crop preparation, along with analytical results of each crop is presented. Complete analytical results of the milk, eggs and meat study is also attached.
2. To compliment our work on metabolism of DMSO, attached is experimental work of Dr. Jöchle, et al of Syntex on bovine using C^{14} tagged DMSO. This work shows rapid metabolism and excretion of DMSO and its metabolites. Comments are also made relative to DMSO's metabolism into natural occurring sulfur compounds in plants and animals.
3. A discussion on potentiation of pesticide residue by DMSO is presented.

We appreciated the opportunity given us to meet with you to clarify the questions regarding this petition. We are looking forward to hearing from you.

Very truly yours,

J. A. CHAPMAN/hw

General Manager
 Chemical Products Division

Attachments

End
of
Document

PP# 4F1486

MEMORANDUM OF CONFERENCE
January 23, 1975

BETWEEN: J.A. Chapman.....Crown Zellerbach Corp.
N.J. Lasater.....Crown Zellerbach Corp.

AND

Dr. G.E. Whitmore.....Toxicology Branch
Charlotte Young.....Assistant Product Manager, Team #25
R. Beyak.....Chemistry Branch
R.S. Quick.....Chemistry Branch

SUBJECT: Outstanding deficiencies in the DMSO proposal, PP# 4F1486.

The petitioner requested the conference to discuss the items outlined in the COB reject letters of 8/2/74 and 12/2/74 (L. Zink). The first item under discussion was the question of the residue composition in meat, milk and eggs as a result of feeding goats and poultry with radiolabeled DMS-³⁵S material. This question was discussed fully in the review memos of R. Beyak (7/24/74) and D.L. Ritter (9/9/74). The deficiency was based upon the following considerations: (1) 65% of the ³⁵S activity in the residues of DMSO in meat, milk, and eggs were not identified, (2) feeding studies with goats and hens at the 20 ppm level of DMS-³⁵S resulted in significant residues of DMSO, per se (determined by ³⁵S activity) in meat (0.2 ppm), milk (0.06 ppm), and eggs (0.3 ppm), and (3) the 20 ppm feeding level may not be an exaggerated dose since we do not have residue data for livestock feed and forage items.

One of the principals, D.L. Ritter, was unable to attend the conference due to illness and Dr. Whitmore, not being familiar with the history of this action, was unable to support the position of requiring the identification of the residue. TB promised to re-review the data.

-2-

We discussed another deficiency regarding our requirement for details of their sample preparation technique employed in the fruit and vegetable residue studies. The petitioner acknowledged the oversight and will submit the necessary information as soon as possible. We discussed the need for DMSO residue data on forage items. While we do not object to the label restriction against applications of DMSO to pasture or range grasses, we still require residue data on forage items (see memo of R. Beyak, 10/22/74). The petitioner agreed to provide us with this information.

As a result of our discussion with the petitioner regarding information on DMSO potentiation of pesticide levels, we agreed that this is a question the registrant of new DMSO-containing formulations will have to answer at the time of registration.

Two other items in the reject letters were not discussed. Environmental data requirements were not considered since a representative from EEEB was not present. In addition, we did not discuss the status of the petition, that is, whether an exemption or a full tolerance proposal should be considered. This discussion was postponed pending TB's secondary review of the data and CB's conclusion of DMSO residue levels on forage items (forage residue data to be submitted, as indicated above).

Richard Beyak
Chemistry Branch
Registration Division

cc:
Product Manager
Tox. Br.
Chem Br.
PP# 4F1486
Recd.
RF

RBeyak:yp: 2/7/75
RD/I-ELGunderson:2/5/75
RSQuick: 1/30/75

Chem Bl.

Rec'd Chem. Div. DEC 9 1974

REGISTRATION DIVISION
December 2, 1974~~Chem. Div.~~
Bayer
PP# 14 & 6

Pesticide Petition No. 4F1486

Mr. J.A. Chapman, General Manager
Crown Zellerbach Corporation
Chemical Products Division
Camas, Washington 98607

Dear Mr. Chapman:

This refers to Pesticide Petition No. 4F1486 proposing the amendment of § 180.1001(d) to permit the use of dimethyl sulfoxide, as follows:

Uses: Solvent, cosolvent.

Limits: Not to be applied within 24 hours of harvest.
Not to be applied to pasture or range grasses grown for grazing after soil emergence.

We have completed our review of this petition as amended August 8, 1974, and find that we cannot act favorably on it for the following reasons:

1. We feel that the residues in fruits, vegetables, and grains represent a toxicologically significant exposure of DMSO in the human diet. Therefore, a full tolerance petition for DMSO for this proposed use (including the 24 hour preharvest interval) is required. (This petition will require a validated residue method for enforcement purposes.)

2. Resolution of points 1, 2, and 3 of our letter of August 2, 1974, is still required. In addition, information or data demonstrating the effect, or lack thereof, of DMSO on the residue levels and the efficacy of the pesticides and/or their metabolites on the raw agricultural commodities is required.

- 2 -

Our Registration Section informs us that environmental data in support of PR Notice 70-15 will be required prior to acceptance of post-emergence uses of DMSO.

Perhaps you should request a conference to discuss these requirements. Please let us have your reply within 30 days.

Sincerely yours,

Libby A. Zink
Ecologist
Coordination Branch

cc: Branch File
Chemistry Branch
Toxicology Branch
EEEB
P. Critchlow

LAZ:el 12/2/74 RDInits Mayes 11/29/74 Williams 11/25/74
Gunderson 11/25/74

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of
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PP#4F1486. Proposed Exemption for Dimethylsulfoxide. Comments on amendment of 8.8/74.

OCT 22 1974

Coordination Branch
Toxicology Branch, RD

The amendment is in response to a reject letter from COB (L.A. Zink, 8/2/74). The COB letter outlined three CB deficiencies in the proposal for an exemption of a tolerance for DMSO when used as a solvent in pesticide formulations.

We will list the deficiencies in the order that they appeared in the reject letter followed by the petitioner's response and our comments. Because the first deficiency is quite detailed, we will reproduce the pertinent section of this deficiency only, for purposes of this review.

1. Deficiency. We need to know the composition of the residue, as determined by total ^{35}S activity, in milk, eggs, and meat tissues. . . .

Response and our comment. No new data are submitted and no explanation to clarify the uncharacterized fraction of the DMSO residues in milk, eggs, and meat is presented. We consider this deficiency unresolved. TB has also expressed a desire to know the identity of the DMSO residues in animals (see memo of D.L. Ritter, 9/9/74).

2. Deficiency. We need to know the details of the sample preparation techniques employed for the fruit and vegetable residue studies.

Response and our comment. No information or details regarding sample preparation techniques used in the residue studies is submitted. This deficiency remains unresolved. We need this information to determine whether or not the preparations actually conform to commercial practice or to the definitions set forth in Section 180.1(j) of the Regulations.

3. Deficiency. We require residue data for forage grasses; data for alfalfa and a representative grass will be adequate.

Response and our comment. The amendment does not contain additional residue data but does contain as amended Section F that includes the additional limitation: "Not to be applied to pasture or range grasses for grazing after soil emergence". Range grasses are not a seasonally cultivated crop but are normally found in various stages of growth. While we

PP#4F1486 Page 2

believe that treatment of grass before soil emergence would be a relatively rare occurrence, imposition of such a restriction would be in line with the restriction in the present regulation and we have no objection to it.

In lieu of submitting forage data, the petitioner argues that the data for peas and soybeans, originally submitted with this proposal, would "be adequate for the forage legume category". In the absence of a specific indication that forage was the commodity actually analyzed, we assumed, then and now, that the pea and soybean data actually referred to the bean (or pea) only.

We consider the petitioner's response to be inadequate and, consequently it does not satisfy our requirements to fulfill this deficiency.

Other Considerations

After a review of our comments on this proposal (memo of R. Beyak, 7/24/74), TB recommended against the establishment of the tolerance exemption (see memo of D.L. Ritter, loc cit). Because of toxicological considerations and the increased DMSO residue levels resulting from the now proposed use, they recommended that a full tolerance petition for DMSO residues would be more appropriate. CB questions whether a tolerance can be established for DMSO as an inert ingredient. The Regulations indicate that tolerances apply to active ingredients. We defer to the Director's Office as to whether a tolerance is appropriate to cover the present proposal. If RD finds that a tolerance proposal is required, then CB will request an enforcement method with adequate sensitivity to enforce the proposed tolerance. The present residue method available for enforcement is sensitive to approximately 3 ppm (see memo of W.J. Boodee, PP#1F1017, 8/28/71). TB has also raised a question regarding the effect of DMSO on the residue levels of the pesticide in the r.a.c. and has deferred to CB on the question of whether DMSO use in pesticide formulations may result in above tolerance residues of such pesticides in r.a.c.s. CB has no data at its disposal to answer this question and we agree that the unique solvent characteristics of DMSO and its ability to enhance the absorption of chemicals presents a possibility that residue levels of the pesticide may be affected.

To answer TB's question, the petitioner should submit information and/or residue data to demonstrate the effect (or lack of effect) on the residue level on representative crops of typical pesticides in the different classes (and their metabolites) as a result of using DMSO in the formulation.

PP#4F1486 Page 3

Conclusions and Recommendations

1. Deficiencies #1 and #2 in the reject letter remain unresolved and the petitioner should be so informed.
2. The response to deficiency #3 is inadequate. We reiterate our requirement for DMSO residue data for representative legume and grass forage items.
3. If the Director's Office finds that a tolerance is appropriate for the proposed use then CB will require a validated residue method for enforcement.
4. Based upon TB's concern, information or data demonstrating the effect, or the lack thereof, of DMSO on the residue levels of the pesticides and/or their metabolites in the r.a.c. will be required.
5. We note that EEEB objects to the post-emergence use of DMSO due to the lack of supporting data (memo of R.J. Ney Jr., 7/29/74).

We suggest a conference be set up with the petitioner to discuss the problems associated with this petition.

Richard Beyak
Chemistry Branch
Registration Division

cc:

Tox.Br.
RO-130(FDA)
P.Critchlow
Ecol.Eff.Br.
Chem. Br.
PP#

RBeyak:gac
10/22/74

RD/I ELGunderson
 RSQuick

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

SUBJECT: Exemption from the requirements of a tolerance for Dimethylsulfoxide (DMSO), CB review of 7/24/74, R. Beyak DATE: September 9, 1974

FROM:

TO: Mr. Lee TerBush, Acting Chief
Coordination Branch
Registration Division (WH-567)

Rec'd Chem. Br. SEP 13 1974

Pesticide Petition No. 4F1486
Related Petitions: 1E1017 & 3E1364

Crown Zellerbach Corp.
Camas, Washington

CB has deferred to TB the question of unidentified residues of DMSO in meat, eggs and milk resulting from this proposed use as a solvent or cosolvent. In our initial review of this petition (memo of 5/2/74, Dr. C. H. Williams) TB concluded that the proposal for clearance of DMSO under 180.1001(d) with a 24 hour PHI could be granted, CB considerations permitting, and that the previous proposal limiting application to "....before formation of edible parts...." was based on CB's estimate that no more 1 ppm residue of DMSO and DMSO₂ could be expected (review of 4/18/73, PP #3E1364, A. Rathman), and was supported by the available toxicity data.

However, Mr. Beyak has concluded:

1. Plant residues are adequately characterized and consist of 85% DMSO and DMSO₂.
2. Proposed use will result in pesticide residues at levels up to 2 ppm in edible portions of fruits and vegetables and at levels up to 6 ppm in grains.
3. The feeding of DMSO to animals will result in residues in meat, eggs and milk; the identification and levels of metabolites are questionable.
4. The sensitivity of the analytical method is only about 3 ppm.

Page 2 - PP No. 4F1486

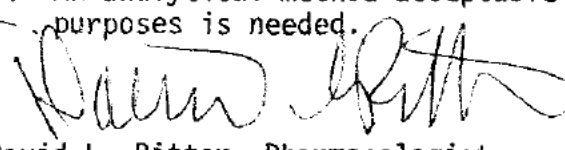
Conclusions

1. TB considers that the question of unidentified residues in plants is adequately answered; we are not concerned further with such residues. Further characterization needed, however, for meat, eggs and milk residues.
2. We consider that 2 ppm residues in fruits and vegetables and 6 ppm levels in grains represents a toxicologically significant exposure of DMSO in the human dietary; accordingly we recommend that serious consideration be given to establishing tolerances for this material rather than granting the proposed exemption. USDA at one time considered that DMSO was an "active ingredient" of pesticide formulations since it could be expected to enhance significantly the activity of the economic poison with which it was to be used (memo of Policy, H. W. Hays, Director, PRD/USDA, 6/6/68). This being the case, we also recommend that consideration be given to the possibility that tolerance levels of pesticides used in conjunction with DMSO might be inadequate by virtue of increased translocation into the plant; e.g., with foliar application.

The propensity of DMSO for enhancing absorption of chemicals across the skin (see literature review of R.P. Schmidt, PP #1E1017, 12/16/71) raises questions as to user/applicator safety from the active ingredient in formulations containing DMSO which must be addressed before we can register any more of such formulations.

Recommendations

1. We recommend that the proposed exemption for DMSO in section (d) with a 24 hour PHI not be granted because of 1 and 2 above.
2. We defer to CB as to whether the use of DMSO in pesticide formulations may result in higher-than-legal residues of such pesticides and/or their metabolites in subject rats.
3. We recommend that petitioner submit a full tolerance petition for DMSO as it is to be used (including the 24 hour PHI).
4. Further characterization of the unidentified metabolites in meat, eggs and milks is needed.
5. An analytical method acceptable to CB for tolerances enforcement purposes is needed.

 9/9/74
David L. Ritter, Pharmacologist
Toxicology Branch
Registration Division (WH-567)

cc: CB ✓ Div. File PP No. 4F1486
EEB Br. File DLRitter/ccw 9/9/74

Init: CHWilliams 
9/9/74

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*Mr. Landolt*FOR OFFICIAL USE ONLY--INDEFINITE RETENTION

UNITED STATES DEPARTMENT OF AGRICULTURE
AGRICULTURAL RESEARCH SERVICE
Pesticides Regulation Division
Washington, D. C. 20250

(*-*)

No. 323

June 6, 1968

To: State Regulatory Control Officials

From: Harry W. Hays, Director

Subject: Registration Policy for Products Containing DMSO

Products containing limited amounts of Dimethyl Sulfoxide have been accepted for registration under the Federal Act.

Consideration will be given to the registration of agricultural products containing up to approximately 15% DMSO. Toxicity information will be required for each formulation proposed, including dermal absorption studies. Since this chemical is likely to enhance the rate of absorption and change the toxicity of the product, toxicity of the specific formulation will be required.

For such products, it will be required that Dimethyl Sulfoxide be declared as an active ingredient since it would be expected to enhance significantly the activity of the economic poison.

If a product containing this chemical is intended for use where food or feed is involved, a tolerance or an exemption from the need for a tolerance established under the Federal Food, Drug, and Cosmetic Act will be required.

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Crown Zellerbach

CHEMISTRY L. NCH

Chemical Products Division

Rec'd Chem. Br. AUG 30 1974

August 8, 1974

Mr. Libby A. Zink
Ecologist
Coordination Branch
Registration Division
United States Environmental
Protection Agency
Washington, D. C. 20460

Dear Mr. Zink:

Re: Pesticide Petition No. 4F1486

We are very disturbed by the contents of your letter of August 2, 1974, regarding the above petition, particularly on your items 1 and 2.

First, after several contacts with your agency regarding required information, it was pointed out to us that residues of pesticide solvents or other adjuvants in animal products are not required but that a simple test to show the lack of accumulation of DMSO in milk would be very helpful. It was our own decision to conduct such studies and to conduct them to the extent that more detail was exacted than could be determined from just a "simple test". We certainly feel that we have demonstrated the lack of accumulation of DMSO and any metabolites in the animal products and have gone well beyond normal requirements for solvents.

Secondly, please consider that the amount of DMS³⁵⁰ fed to the animals was highly exaggerated in that the daily dosage was equivalent to 20 ppm of the total solids diet of the animals. One would expect from our results that between 0.01 and 5 ppm DMSO would be present in the crops if fed the same day as harvested. If the diet having residues of DMSO contained only 20% of crops (a more likely level), the 20 ppm level is in the range of 20 to over 10,000 times greater than would actually exist. Perhaps this was not made clear in the petition and I would like to have you consider this point.

Your item #2 asks for details on sample preparation. Pages 3 through 13 of the Field Crop Procedure section discusses the procedures showing Peach as an example. In protocol discussions,

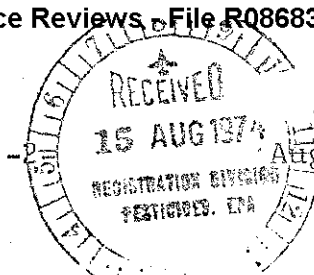
45th DAY

10/11/74

~~Gunderson~~
Nelson
BEyak
PP# 4F1486

TORRER review
8/30/74 by mjm

Mr. Libby A. Zink



August 8, 1974

we were told by your agency that it was acceptable and preferable not to include every crop in the procedures and to use references to procedures in previous petitions as much as possible. We have followed this advice in this petition.

As far as residue data on alfalfa is concerned, we did not include it in the study. We assumed data on pea and soybean would be adequate for the forage legume category. As far as forage grasses are concerned, we would expect the residues to be in the same range as small grain, as experienced in the study shown in Petition 3E1364. However, if you insist that actual data be collected before favorably acting on the proposed amendment, we would be agreeable to making pasture and range grasses an exception until we can gather such required information.

Therefore, we would be agreeable to changing the proposal to:

Uses: Solvent, cosolvent

Limits: Not to applied to crops within 24 hours
of harvest. Not to be applied to pastures
or range grasses, grown for grazing after
soil emergence.

At this point, I do not believe this will cause a problem as far as pesticide firms are concerned and we would want to assess the value of seeking further approval on forage grasses before resuming research.

We honestly feel that we have clearly demonstrated that the use of dimethyl sulfoxide as a pesticide solvent is safe in light of its toxicity and potential residues. If after considering the above, you are not satisfied, please give me a call. I would like to set up an interview with you.

Very truly yours,

General Manager
Chemical Products Division

J. A. CHAPMAN/hw

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~~Anderson~~
Beyak
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ENVIRONMENTAL CHEMISTRY EVALUATION FOR [Dimethyl Sulfoxide]

PP No. 4F1486

Reg No.

Crown Zellerback

I. INTRODUCTION

Dimethyl sulfoxide (DMSO) has been certified as a useful solvent in pesticide formulations. This chemical has been considered an inert ingredient in pre-emergence application. The petition for its use within 24 hours of harvest brings this special review.

II. DIRECTIONS FOR USE

To be used as a pesticide solvent. Its concentration may be such that its application is between .5 and 5 pounds per acre.

III. RECOMMENDATION

- (A) Object to post emergence use of products containing DMSO and/or the inert ingredient DMSO.

1. A review of this submission cannot be made because chemistry data support of PR Notice 70-15 has not been submitted. It is determined that these data are needed for any post emergence application of a product containing DMSO. See enclosures

Pat Critchlow enclose Second Draft of Guidelines

RECEIVED 8/6/74
Ronald E. Ney
Joe Boyd
Environmental Chemistry Section
Efficacy and Ecological Effects Branch

gjl:8/5/74

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L. Zink

REGISTRATION DIVISION

August 2, 1974

Pesticide Petition No. 4F1486

Mr. J.A. Chapman, General Manager
Crown Zellerbach Corporation
Chemical Products Division
Camas, Washington 98607

Dear Mr. Chapman:

This refers to Pesticide Petition No. 4F1486 proposing the amendment of § 180.1001(d) to permit the use of dimethyl sulfoxide, as follows:

Uses : Solvent, cosolvent.

Limits: Not to be applied within 24 hours of harvest.

We have completed our review of this petition and find that we cannot act favorably on it for the following reasons:

1. We need to know the composition of the residue as determined by total ^{35}S activity, in milk, eggs, and meat tissues (excluding fat and goat liver) from the ingestion of ^{35}S -labeled dimethyl sulfoxide; based on these results, we may require further identification of uncharacterized residues in these items.
2. We need to know the details of the sample preparation techniques employed for the fruit and vegetable residue studies.
3. We require residue data for forage grasses; data for alfalfa and a representative pasture grass will be adequate.

- 2 -

We may have additional comments regarding soil persistence upon completion of environmental data review.

Upon receipt of the required residue data and other required information, we will be able to give further consideration to this petition. Please let us have your reply within 30 days.

Sincerely yours,

Libby A. Zink
Ecologist
Coordination Branch

cc: DMBaker
Branch File
Chemistry Branch
Toxicology Branch
EEB
P. Critchlow

LZ:el 8/2/74 RDInits: Gunderson 7/27/74 Williams 7/29/74 Gross 7/29/74
TerBush 7/30/74

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

SUBJECT: Proposed Exemption for Dimethylsulfoxide. Chemistry DATE: July 24, 1974
Evaluation

FROM:

TO: Coordination Branch
and Toxicology Branch, RD

Crown Zellerbach Corporation is proposing the establishment of an exemption from the requirement of a tolerance (Sec. 180.1001) for residues of dimethylsulfoxide when used as a solvent or cosolvent in pesticide formulations not to be applied within 24 hours of harvest. The current exemption for the residues of DMSO limits the use as a solvent for formulations used before crop emerges from soil or prior to formation of edible parts of food plants.

Proposed Use

The present proposal is directed to the general use of DMSO as a solvent rather than a specific formulation. However, in general the amount of DMSO to be applied will normally be in the range of 0.5 lb. to 5 lb. per acre. Occasionally, the usage rate may exceed this figure, as, for example, with pesticides applied on heavy clay soil, hence, no finite limit is given.

Analytical Methods

The radiochemical analytical procedure for crop materials is similar to that described in the previous proposals (PP# 1E1017, 3E1364). However, minor modifications were introduced to increase the sensitivity for various crops. Allowance was made to correct for the DMS³⁵O specific activity for each crop since the activity varied according to the amount applied. In addition, corrections for ³⁵S decay were made for calculating individual counting data and the specific activity due to the wide intervals of harvesting and analyzing. A combination of scintillation spectroscopy of solids digests and extracts and TLC were used to separate DMS³⁵O and the metabolites on all crops and animal tissues. Briefly, this procedure involves the following: (1) determining the total ³⁵S in the plant at harvest by nitric acid digestion, (2) extracting DMS³⁵O from the plant solids with aqueous ethanol, and (3) separating and identifying the ³⁵S compounds in the extract by TLC. Recoveries on DMS³⁵O crop extracts were previously reported in PP# 3E1364.

PP# 4E1486--Page 2

The radiochemical analytical procedure for the determination of DMS³⁵O in animal tissue, milk and eggs is identical to the method described above with one exception. The nitric acid digestion of crop material in the determination of total ³⁵S activity is replaced by an alkaline digestion step.

Recoveries of DMS³⁵O on milk, eggs and hamburger were reported at 87.2%, 91.4%, and 121.3%, respectively. The limit of detectability was reported at <0.01 ppm.

A regulatory method involving GLC analysis with flame ionization detection was previously submitted, however, CB concluded that the method was adequate for purposes of detecting instances of gross misuse only (sensitivity about 3 ppm). Therefore, we recommended at that time and reiterate now that an MTO will be necessary should higher sensitivity be required (see memo of W.J. Boodee, PP# 1E1017, 8/28/71).

Residue Data

Plant residue data are submitted for eleven crops which were selected to represent the major food crop groupings of: curcurbits (cucumbers); fruiting (tomato), leafy (cabbage), root crop (onion), and seed and pod vegetables (sweet peas and soybeans); pome (apple), small (raspberry), and stone fruits (peach); grain crops (barley and corn); stored commodities (dried beans); and cotton. The crops were field grown at Washington State University at Vancouver, Washington, with the exception of cotton and soybeans, which were maintained to maturity in a greenhouse. All crops received a single treatment of DMS³⁵O, at a rate of 5 lb./A, 24 hours before harvest. As each crop was harvested, the excess soil and foliage were removed in accordance with standard commercial practice (no further details are given).

Analyses by the radiochemical procedure detected maximum DMSO residues (as total ³⁵S activity) for barley, raspberry and peach at 5.4 ppm, 1.8 ppm and 0.37 ppm, respectively. All other results were reported at less than 0.1 ppm, including DMSO residues on cabbage at <0.01 ppm.

Little information is given on sample preparation technique and since this proposal covers a wide variety of different crops, we require a more detailed description of the sample preparation for each crop. We will need this information to determine whether or not the preparations actually conform to commercial practice or to the definitions set forth in Section 180.1(j) of the Regulations. We are especially concerned about the low residue level reported for cabbage. In addition, since the proposed use of DMSO as a solvent in pesticides will undoubtedly be used on forage items, we would like to examine residue data for the forage groupings of grasses and legumes reflecting DMSO treatments at the proposed use rate. Data from the previous DMSO petitions (PP# 1E1017 and 3E1364), reflecting pre-emergence treatments and/or applications prior to the formation of any edible parts, cannot be used to support the present proposal since the proposed use is limited to applications up to

PP# 4F1486-Page 3

24 hours before harvest.

We conclude that additional residue data for forage crop groupings and more information regarding sample preparation are needed before we can determine what the expected residue level will be from the proposed use of DMSO.

Results of two 28-day animal feeding studies are submitted. One study at Oregon State University was carried out with a dairy goat and another at Washington State University with three hens. A daily dosage of dimethyl sulfoxide (labeled with ^{35}S) was fed to each animal at a level of 20 ppm in the total solid diet. While milk and egg samples were taken daily, the samples taken every fifth day were analyzed for total ^{35}S activity and DMS^{35}O activity (via TLC separation). The animals were sacrificed 24 hours after the last dosage of DMS^{35}O was administered. The previously described radio-chemical procedure was used to analyze the poultry and goat tissues.

Residues were determined by total ^{35}S activity counts (expressed as DMSO) and were reported at maximum levels of 0.64 ppm in milk, 3.0 ppm in eggs, 3.85 ppm in goat liver and 2.1 ppm in poultry liver. An analysis of the total ^{35}S activity fraction in goat liver tissue was reported to be a mixture of dimethyl sulfoxide, dimethyl sulfone and an unidentified component referred to as "higher molecular weight materials" with an approximate 1:1:4 distribution ratio. The "higher molecular weight materials" actually consist of a series of constituents that chromatographed before, after and in between the DMSO and DMSO_2 fractions on TLC.

Since only 32% of the total ^{35}S activity in the goat liver is extractable and of this 32% only 34% has been identified, we will require information as to the amount of unidentified fractions in the other substrates. Based upon these data, we may require additional identification of the unknown constituents if TB concurs.

As a result of TLC determinations on extracts, DMSO residues were reported at maximum levels of 0.06 ppm in milk, 0.28 ppm in eggs, 0.20 ppm in goat liver, and 0.44 ppm in poultry liver. DMSO residues were 0.09 ppm in goat muscle and 0.2 ppm in chicken muscle. No DMSO residues were found in the fat of the animals at a 0.01 ppm sensitivity level. The residue results of the daily milk and egg samples taken during the feeding period did not indicate a buildup of DMSO residues but maintained a relatively constant level of 0.05 ppm and 0.20 ppm, respectively.

In summary, we conclude that additional information is needed regarding the amount of unidentified ^{35}S material in milk, eggs, and animal tissues (excluding goat liver). Based upon these results and TB's concern, we may require additional identification of the unknown DMSO residues.

PP# 4F1486-Page 4

Conclusions

- 1(a) The nature of the DMSO residue in animals is not adequately understood. Only 34% of the extractable ^{35}S activity found in the goat liver residue has been identified as DMSO and its sulfone. We will require information or data as to the extent of the unidentified fractions in milk, eggs and other tissues.
- (b) The nature of the DMSO residue in plants has been adequately delineated. The major portion of the residue (>85%) is DMSO and its sulfone.
- 2(a) The proposed use of DMSO as a solvent in pesticide formulations will result in residues not to exceed 2 ppm on the edible portions of fruits and vegetables and 6 ppm in small grains. This conclusion is contingent upon a review of the sample preparation technique for these crop items.
- (b) There are no residue data to support the use on forage items.
3. An analytical method is available for enforcement purposes; however, the sensitivity is sufficient to detect instances of gross misuse only (ca. 3 ppm).
4. The ingestion of DMSO residues by livestock results in the transfer of residues to meat, milk, poultry and eggs. The feeding of 20 ppm DMSO in the diet of goats and ~~sheep~~^{poultry} resulted in:
 - (a) Total residues (activity calc. as DMSO) of ca. 0.7 ppm in goat milk, 4 ppm in goat liver, 2.5 ppm in goat kidney and 0.75 ppm in muscle and fat. Of these residues, DMSO per se constituted a maximum of 0.06 ppm in milk and 0.2 ppm in tissues.
 - (b) Total residues (calc. as DMSO) of 3 ppm in eggs, 2 ppm in chicken liver and <1.5 ppm in chicken muscle and fat. Of these, DMSO per se constituted a maximum of 0.3 ppm in eggs and 0.5 ppm in tissues.

Recommendations

We recommend against the proposed exemption.

For a favorable recommendation, the petitioner should be advised of the following:

- (1) We need to know the amount of unidentified residues, as determined by total ^{35}S activity, in milk, eggs, and meat tissues (excluding goat liver) and based on these results (and TB's concern), we may require further identification of the unidentified residue.

NT 471486 Page 1

- (2) We need to know what sample preparation techniques were employed for the fruit and vegetable residue studies.
- (3) We require residue data for representative forage items. We defer to you regarding the question of soil persistence and the need for crop rotation restrictions.

R. B. per XTC
Richard Beyer
Chemistry Branch
Registration Division

cc:
Tox. Gr.
HEHS
RD-3130 (FDA)
P. Critchlow
Glasgow
PP# 471486
CB
RF
Beyer.

RBeyer:yp. 7/23/74
RD/1-ELGanderson: 7/22/74
RSQuick: 7/15/74

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

CB

SUBJECT: Dimethylsulfoxide (DMSO) - Exemption from requirement of a tolerance. DATE: May 2, 1974

FROM:

Rec'd Chem. Br. MAY 7 1974

TO: Mr. Lee TerBush
Acting Chief
Coordination Branch
Registration Division (HM-567)

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#1486

Pesticide Petition No.: 4F1486

- Crown Zellerbach Corporation
Chemical Products Division
Camas, Washington 98607

The petitioner has submitted this petition to amend the existing 180.1001(d) exemption from tolerance requirement for DMSO regarding the uses and limits. The present exemption, established August 13, 1973, limits the DMSO to a solvent or co-solvent for formulations to be applied before the crop emerges from the soil or prior to formation of edible parts of food plants. The present request is for DMSO to be used as a solvent or co-solvent in pesticidal formulations which can be applied up to 24 hours of harvest.

No new toxicity data was submitted. A reference was made to previous petition 1E1017. A statement was furnished that DMSO was removed from the National Institute for Occupational Safety and Health's 1973 toxic substances list. This list contains 11,000 different chemicals considered potentially toxic under criteria established by NIOSH. Petitioner also submits a draft of a report from the New York Academy of Sciences Conference on Biological Actions of DMSO, January 11, 1974. This is a clinical study on mentally retarded children with DMSO. In the summary of this article it is stated that the only significant changes during treatment with DMSO were two children who developed unexplained anemias thought not to be related to the administration of the DMSO. Since the study has not been completed, and it is a double-blind study the dosages administered are not available.

In August of 1973 an Ad Hoc Committee of the National Academy of Sciences National Research Council, Division of Medical Sciences, released a report on dimethylsulfoxide. This report was entitled Dimethylsulfoxide as a Therapeutic Agent and had been requested by the Food and Drug Administration. The conclusion of this committee relevant to our considerations for an exemption from a tolerance on food crops is "in

Page 2 - PP# 4F148

some species of laboratory animals, DMSO in doses somewhat higher than those contemplated for man produces a unique alteration of the lens. The effectiveness of DMSO is not such as to warrant the release of the drug for prescription in general medical practice at this time." In other words large therapeutic doses of DMSO are not recommended. However, the levels of DMSO which would be available from the proposed exemption would be a much lower range than would be used for therapeutic purposes. No-effect levels from toxicity studies in dogs and in monkeys are in terms of g/kg whereas the residues on the crops, according to the petitioner, would be a maximum of about 5 ppm (fall barley).

The toxicity data in PP# 1E1017 and PP# 3E1364 were reviewed by Dr. R. P. Schmidt and his favorable recommendation was based upon CB's finding (memo of A. Rathman, 5/18/73) in which he stated that CB would not expect combined residues of DMSO and DMSO₂ to exceed 1 ppm in crops. At that time the residue levels in meat and milk were calculated ones.

Present petition contains further residue data. The residue levels which the petitioner claims he finds in goat tissue and milk and eggs and poultry tissue and in the crops tested for residues, are supportable by the toxicity data which are in TB's files for DMSO. However, we must await CB's evaluation of the residue data and their concurrence with the petitioner's claims.

Recommendation

CB's considerations permitting, we recommend that the exemption from a tolerance for DMSO as established previously under 40 CFR § 180.1001(d) be amended as proposed by the petitioner.

Clara H. Williams

Clara H. Williams, Ph.D.
Chief
Toxicology Branch
Registration Division (HM-567)

cc: CB ✓
EEB
Division File
Branch Reading File
PP# 4F1486

CHWilliams:sss:5/2/74

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Rec'd Chem. Br. MAY 3 1974
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#1486

Registration Division

April 26, 1974

CERTIFIED MAIL

Mr. J. A. Chapman
Crown Zellerbach Corporation
Chemical Products Division
Camas, Washington 98607

45th DAY 6/10/74

Dear Mr. Chapman:

Pesticide Petition 4F1486 proposing an exemption from the requirement of a tolerance for residues of the solvent dimethyl sulfoxide when used in accordance with good agricultural practices on raw agricultural commodities prior to harvest was filed April 10, 1974.

We have examined this petition for certification purposes and are certifying that the solvent is useful for the purpose for which an exemption from the requirement of a tolerance is sought.

Further action awaits completion of scientific review and evaluation.

Sincerely,

Lee E. TerBush
Acting Chief,
Coordination Branch

EPA:RD:SX:PCCritchlow:lms 4/26/74

cc: Coord. Br.
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TB
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Chemistry Branch

CBAPR 15 1974

REGISTRATION DIVISION
April 10, 1974

Pesticide Petition No. 4F1486

Mr. J.A. Chapman, General Manager
Crown Zellerbach Corporation
Chemical Products Division
Camas, Washington 98607

Dear Mr. Chapman:

This acknowledges receipt of your letter of March 20, 1974,
the certified check for \$2,000, and the petition proposing
that § 180.1001(d) be amended regarding uses and limits of
dimethyl sulfoxide, as follows:

Uses: Solvent, cosolvent.

Limits: Not to be applied within 24 hours of
harvest.

The petition has been designated Pesticide Petition No.
4F1486 and it is being filed today. Further action awaits
completion of scientific review and evaluation.

Sincerely yours,

Libby A. Zink
Biologist
Coordination Branchcc: OMBaker
Branch File
Chemistry Branch
Toxicology Branch
EEB
P. Critchlow

LZ:el 4/10/74 LET 4/9/74



13544

R086836

Chemical: Dimethyl sulfoxide

PC Code: 900177

HED File Code 11500 Petition Files Chemistry

Memo Date: 01/06/2004

File ID: 00000000

Accession Number: 412-05-2000

HED Records Reference Center
08/31/2004